ARCHIVES OF PATHOLOGY

VOLUME 39 MAY 1945 NUMBER 5

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CHRONIC EXUDATIVE AND INDURATIVE PNEUMONIA DUE TO INHALATION OF SHELLAC

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CHICAGO

Purified lac, one of the natural resins known commercially as shellac, is a basic constituent of various lacquers and oil and spirit varnishes used in the industries as finishing substances. Among the solvents for the lac are methyl alcohol, butyl alcohol, amyl acetate and turpentine. Serious effects from exposure to sprays of these solvents and the dissolved ingredients may follow inhalation into the lungs. Both solute and solvent have importance. When the solvent is simple, such as methyl alcohol, its significance as a noxious agent is small, but when it is an oil, such as turpentine or linseed oil, the importance of the solvent is greater because it contains mixtures of fatty acid compounds, possibly changed by hydrolysis or oxidation at the time of inhalation or later in the tissues of the lungs. The fatty acids resulting from these chemical changes are known to have deleterious effects on animal tissues.

The composition of lac, a natural resin of insect origin, according to Bhattacharya,[1] depends on several factors, among them the brood of the scale insects, the plant serving as host, the climatic conditions and the method of collection. The purified product is not uniform in chemical composition. Stick lac, the resinous incrustation removed from the twigs, contains dead insect bodies, the lac dye and wax, and the true resin constituents. Most of the impurities except wax are removed in processing the shellac. Exclusive of traces of free fatty acids and dye stuff, which are difficult to remove, purified and dewaxed lac resin consists of an ether-soluble and an ether-insoluble resin. The latter is known as pure lac resin. Some evidence favors the view that the component resins of the original lac are bound together in a complex form or a weak chemical linkage. This original relationship when disturbed during purification is not restored. The pure lac resin, constituting 70 per cent of the ordinary lac, consists of hydroxy acids of the aromatic and aliphatic series joined together by lactone and various internal ester linkings. Alcohols have not been detected. Only two of the constituent acids in pure lac resin have been isolated and identified; they are (1) aleuritic, a trihydroxypalmitic acid (melting point 100 to 101 C),[2] forming about 30 per cent, and (2) shellolic, which, according to Harries and Nagel, is a dibasic dihydroxyhydroaromatic acid (melting point 200 to 201 C.), comprising about 10 per cent. The other 50 to 60 per cent of the pure lac resin consists of unidentified acids or, according to Harries and Nagel, hydroxy acids similar to shellolic. Some unsaturated acid is present in lac, according to Bhattacharya, contained in the unidentified 50 to 60 per cent. Barnes[3] reported that the ether-soluble portion of the purified lac consists of polymers of aleuritic and shellolic acids of low molecular weights. The analysis of shellac by Gibson[4] records an acid value of 65 to 75, an ester value of 150 to 163, an iodine value of 18 to 20 and a saponification number between 225 and 231. Saponification numbers of various fractions reported by Schaeffer, Weinberger and Gardner[5] ranged from 147.2 to 342.4. They concluded that most of the compounds of shellac are interesters (including lactides) of the constituent polyhydroxy acids. These statements on the chemical composition of purified lac disclose that the material is a mixture of fatty acids. Some of these acids have been isolated and their structure approximated, but others have not been identified.

From the Henry Baird Favill Laboratory of St. Luke's Hospital.

1. Bhattacharya, R.: J. Soc. Chem. Indust. **54**:82, 1935.

2. Harries, G., and Nagel, W.: Chem. Abstr. **16**: 3070, 1922; **17**:1007, 1923.

3. Barnes, C. E.: Indust. & Engin. Chem. **30**:449, 1938.

4. Gibson, A. J.: Chem. & Indust. **62**:346, 1943.

5. Schaeffer, B. B.; Weinberger, H., and Gardner, W. H.: Indust. & Engin. Chem. **30**:451, 1938.

The reaction of tissues to lipids containing fatty acids has been described in many publications.[6] Among the conclusions recorded are several of significance. Chaulmoogra oil[7] or its mixed esters causes extensive destruction and fibrous induration of the lungs. Tissue reactions[8] to oils introduced into the lungs are related to the speed of hydrolysis and the amount of free acid liberated in the tissues. Animal oils produce necrosis, fibroplastic reactions and giant cells in tissues because of the rapid hydrolysis, and the scar tissue reaction caused by chaulmoogra oil is due to the high fatty acid content of that oil. Products of cod liver oil becoming insoluble in ordinary fat solvents result from oxidation changes similar to those occurring in drying oils. The specific chronic granulation tissues produced in tissues involved in tuberculosis are caused mainly by the lipids[9] contained in the tubercle bacilli. Lipids containing oleic acid[10] cause marked necrosis and fibroplastic reactions in tissues. Gerstl and Tennant[11] observed that fatty acids with nineteen to twenty carbons produced necrosis, but as the length of the carbon chain increased, the tissue response became a proliferative reaction with formation of giant cells. The necrotizing property of a methyl group in various portions of the carbon chain diminished as the length of the carbon chain increased.

Some information concerning the chemical reactions occurring at the interphase of fatty acids and aqueous systems containing dissolved basic compounds was obtained from the experiments of Langmuir and Schaefer[12] and those of Hartsuch.[13] Langmuir and Schaefer found that fatty acids floating on the surface of solutions of calcium and barium salts were converted to corresponding soaps, depending on the p_H of the aqueous medium. Hartsuch reported similar results with solutions of magnesium phosphate and observed an appreciable transfer of magnesium from the aqueous solution to the oleic acid when the p_H of the water medium was 7.0. An equivalent amount of hydrogen ions passed from the oil phase into the aqueous medium, tending to change the reaction to acidity. The reaction between such fatty acid–aqueous systems, of course, is toward an equilibrium, and where the fatty acid is in excess, the p_H of the aqueous medium shifts toward maximum acidity, which for oleic acid is approximately p_H 5.7. Other fatty acids in contact with aqueous mediums probably react in a similar way when in excess, producing in the aqueous medium an acidity probably approaching the hydrogen ion level of oleic acid. Local acidity developed in tissues by fatty acids would seem significant in regard to the necrosis of the tissues and the subsequent inflammatory reaction. Evidence from many sources, accordingly, supports the view that fatty acids in human and other animal tissues cause necrosis and reactive changes ranging through cellular exudation, fibroplastic response and giant cell formation.

Tradesmen working with sprays of varnish, lacquer and shellac may inhale finely divided particles of these finishing substances. Little has been published on the harmful effects of lac substances although there are reports of irritations of eye and nose among workers with shellac sprays and also of some craftsmen who stopped working because of the effects of the sprays.

REPORT OF A CASE

A white man aged 59 years entered St. Luke's Hospital, Chicago, May 13, 1942 in the care of Dr. Paul Holinger because of a chronic nonproductive cough, tiredness and weakness for several years, increasing dyspnea for nine months and a loss in weight of 20 pounds (9 Kg.). He owned a furniture factory and had been exposed to wood dust and varnishes for many years. Roentgen films of the chest taken six years before admission evidenced diffuse density in the base of each lung. Later he was treated for pneumonia. His dyspnea continued and became worse. Examinations at the hospital demonstrated inspiratory rales in both lungs and slight enlargement of the heart. His blood pressure was 150 mm. of mercury systolic and 90 mm. diastolic. A fungous infection or a tumor of the lung was considered possible. The number of leukocytes per cubic millimeter of blood ranged between 12,000 and 15,000. The findings from other examinations of the blood were within the normal range. Nothing significant was disclosed by examinations of the sputum. Roentgen films of the kidneys, the stomach, the bowel and the bones had no unusual shadows, but those of both lungs evidenced extensive infiltrations, especially of the right lung. Bronchoscopic examination demonstrated a thick tracheal and bronchial mucosa and rigid bronchial walls. The electrocardiographic tracings indicated damage of the myocardium. Analyses of the gases of the blood demonstrated interference with pulmonary aeration, and this was considered to be the cause of the dyspnea. After two weeks of discontinuous administration of oxygen, potassium iodide and mapharsen therapy, the patient's cough became much worse and productive. The fever continued, the dyspnea became severe, and death occurred on the twenty-second day after admission.

The essential portions of the anatomic diagnosis based on the postmortem examination (trunk and neck) are: marked chronic indurative pneumonia of both lungs;

6. Hirsch, E. F.: Arch. Path. **31**:516, 1941.
7. Read, B. E.: J. Biol. Chem. **62**:515, 1924. Englebreth-Holm, J.: Klin. Wchnschr. **13**:1605, 1934. Frazier, C. N., and Chen, F. K.: Philippine J. Sc. **42**:269, 1930.
8. Pinkerton, H.: Arch. Path. **5**:380, 1928.
9. Sabin, F. R.; Dean, C. A., and Forkner, C. E.: J. Exper. Med., 1930, supp. 3, p. 1.
10. Haggerty, C.: Arch. Path. **25**:24, 1938.
11. Gerstl, B., and Tennant, R.: Yale J. Biol. & Med. **15**:347, 1942.
12. Langmuir, I., and Schaefer, V. J.: J. Am. Chem. Soc. **58**:284, 1936.
13. Hartsuch, P. J.: Arch. Path. **25**:17, 1938.

fibrinous pleuritis on the right side; fibrous pleuritis on the left side; hyperplasia of parabronchial, cervical and biliary lymph nodes; slight chronic fibroplastic myocarditis; nephrosclerosis and cortical retention cysts of the kidneys; atherosclerosis of the aorta and of its main branches.

The markedly consolidated right lung weighed 1,210 Gm.; the similar left lung, 1,180 Gm. There were no adhesions on the right side between the lung and the chest, but on the visceral pleura there was a thin layer of fibrin. The lung tissues were extensively consolidated diffusely and also in nodules. Surfaces made by cutting had dilated air passages and consolidated parenchyma. These firmly consolidated lung tissues were gray and gray-red, with some portions of a faintly yellow cast and granular (fig. 1). The pleura of the left lung had scattered torn fibrous tissue adhesions. The consolidation of the lung was like that of the right. The heart weighed 400 Gm., and in the myocardium were small regions of gray fibrous tissue. The viscera otherwise had slight or no noteworthy changes.

Fig. 1.—Photograph illustrating the consolidation of the human lungs. The pleural surface of the right lung had a thin fibrinous exudate.

The histologic preparations of the lungs demonstrated extensive oganizing pneumonia (fig. 2). Large portions of the right lung were vascular and had moderately edematous fibrous tissue merging with the parenchyma, into whose alveolar spaces extended edematous fibrillar connective tissues, to some extent replacing the alveolar walls or leaving them as septums of hyperemic capillaries with a small amount of supporting stroma. At other levels these fibroplastic tissues were continuous into regions with alveoli whose lumens contained small masses of fibrillar connective tissues or alveolar spaces filled with granular precipitates, polymorphonuclear leukocytes and variable numbers of mononuclear phagocytes. In many places the polymorphonuclear leukocytes were in excess, and the dilated and modified alveolar spaces and bronchioles contained dense collections of these exudate cells. The lining epithelium of some bronchioles had been changed into squamous epithelium. The walls of the bronchioles were thickened by edematous vascular fibrous tissues or fibrous tissues with exudates of lymphocytes and plasma cells. Some alveolar spaces contained mainly fibrin; others, red blood cells, a moderate number of polymorphonuclear leukocytes and a few mononuclear phagocytes. The indurative and inflammatory changes involved most of the lung parenchyma. A few alveolar spaces had hyperemic walls, lumens with granular precipitates and a few desquamated lining cells or mononuclear phagocytes.

The tissues from the left lung were similar. Several of the large blood vessels contained dense masses of fibrin and red blood cells with leukocytes like a thrombus

but without organization. The leukocytic exudative inflammation was especially marked in this lung and afforded little clue as to the character of the inflammatory agent excepting that in some of the aggregates of polymorphonuclear leukocytes and also in other tissues there were numerous small round vacuolated spaces

no appreciable component of the tissue reactions. The large air passages had lumens with masses of polymorphonuclear leukocytes and a small number of mononuclear phagocytes. Lung tissues fixed in solution of formaldehyde, sectioned by the freezing method and stained with sudan III demonstrated in the exudates and

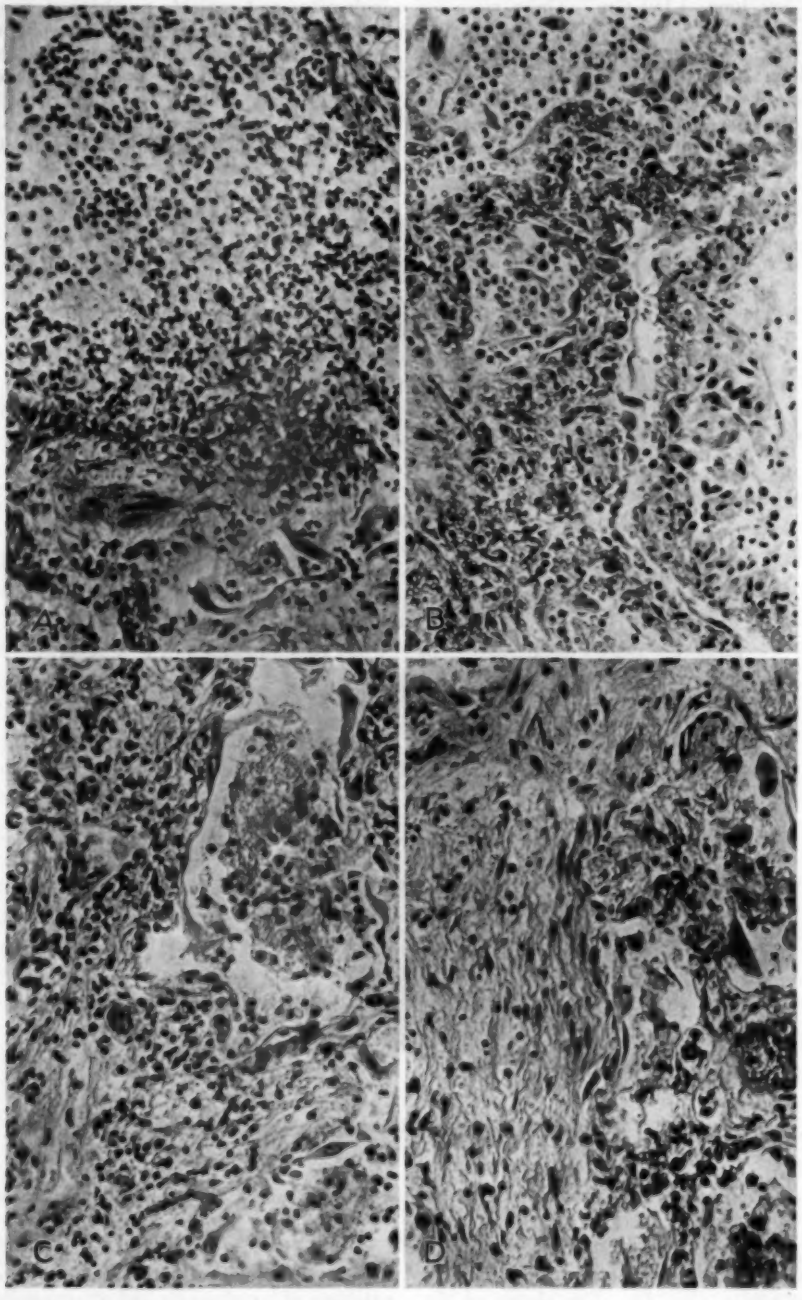

Fig. 2.—Photomicrograph illustrating the exudative and indurative pneumonia of the human lungs; × 198. *A*, dilated alveoli filled with masses of polymorphonuclear leukocytes and fibrin. Small vacuoles are faintly visible in the exudates. *B*, alveoli with exudates and lung parenchyma with fibroplastic tissues. *C*, lung parenchyma replaced by fibroplastic tissues with cellular exudates. Some of the fibrillar tissues have small vacuoles. *D*, alveoli filled with edematous fibrillar connective tissue, and others markedly changed and with exudate cells.

where some liquid substance had been removed in the preparation of the sections. These presumably were the places which in sections stained with sudan III contained quantities of lipoid material. Giant cells were in some of the fibroplastic tissues clusters of lipid globules and macrophages laden with lipoid material.

Forty-five grams of the lung tissues fixed in solution of formaldehyde were extracted with alcohol and ether.

The extract yielded a viscous brown oily residue of approximately 2 Gm. weight. Titration with tenth-normal sodium hydroxide disclosed no free acid. A saponification number of 178 was obtained after hydrolysis with alcoholic potassium hydroxide. The oily residue dissolved in ethyl alcohol, ether, benzine and acetone. It dried slowly to a viscous adherent mass without a surface film like a drying oil. A sample of linseed oil was insoluble in ethyl alcohol but dissolved freely in ether, turpentine and benzine. Accordingly, the material extracted from the lungs seems to be a lac substance in an oil solvent. Alcohol and ether extraction of other portions of the lungs yielded quantities of similar material.

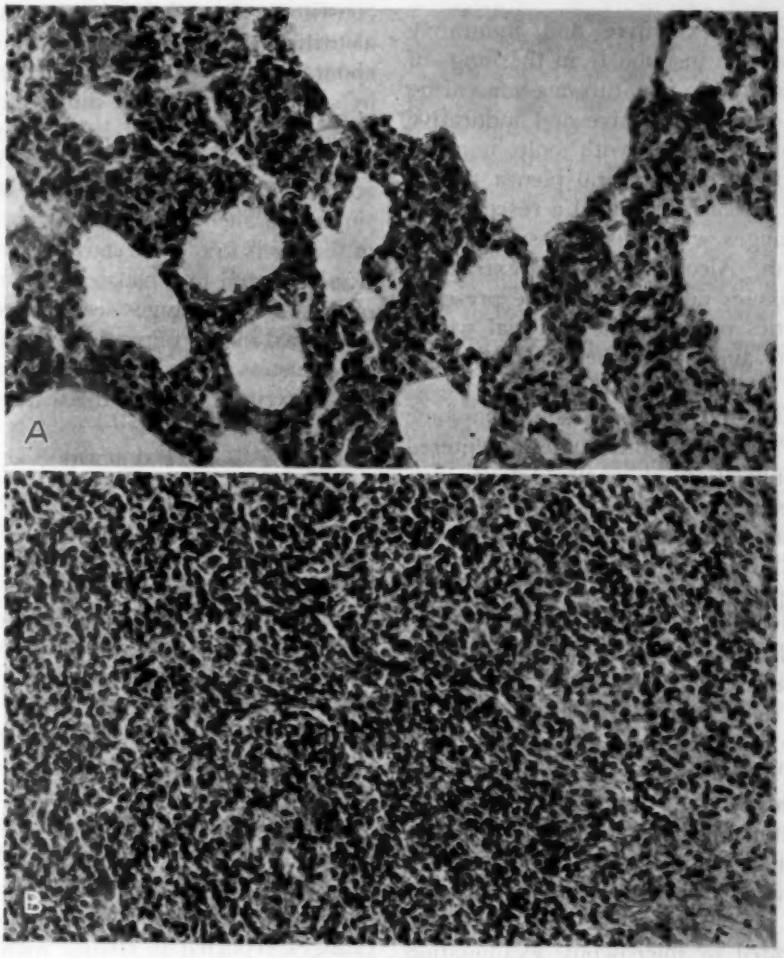

Fig. 3.—Photomicrograph illustrating changes in the lungs of rabbits three months after intratracheal injection of a 5 per cent emulsion in glycerin of, *A*, commercial shellac and, *B*, a laclike material recovered from the tissues of human lungs; × 198.

A 5 per cent solution of the viscid residue in 95 per cent ethyl alcohol was emulsified in nine parts of glycerol. A similar emulsion was prepared with the viscid brown residue obtained by evaporation of the methyl alcohol solvent of a commercial shellac varnish. Quantities of these emulsions ranging from 0.5 to 2 cc. were injected intratracheally into the lungs of rabbits. The lungs of these animals were examined for tissue changes at intervals between one and ninety days. After gross examination the lung tissues were fixed in Zenker's solution for the preparation of hematoxylin-eosin stained sections and in a solution of formaldehyde for the preparation of sections stained with sudan III.

Emulsions of the commercial shellac material in twenty-four hours caused hyperemia and multiple hemorrhages in the lungs. After seven days the lungs had scattered tan-brown nodules composed of alveolar spaces filled with exudates of polymorphonuclear leukocytes, large vacuolated macrophages and foreign body giant cells. The lumens and the walls of the bronchi showed similar exudates. Preparations stained with sudan III demonstrated globules of lipoid material in the alveolar spaces and in the macrophages. The inflammatory changes were more marked after nine days, and after forty-four days the regions of consolidated lung tissues had foci of necrosis, leukocytic exudate cells, fibroplastic tissues, macrophages with lipoid material and foreign body giant cells (fig. 3 *A*).

The tissue reactions in the lungs of rabbits receiving intratracheal injections of the emulsified viscid laclike material recovered from human lungs were much more marked. After seven and eight days there was marked hyperemia of the bronchi, and the lungs had many large firm tan-brown nodules. The histologic preparations demonstrated marked necrosis of the lung tissues. The alveolar spaces contained exudates of polymorpho-

nuclear leukocytes, fibrin, many epithelioid cells, giant cells and large vacuolated macrophages. Sections stained with sudan III showed scattered deposits of lipoid material among the exudate cells and had macrophages filled with lipoid particles. The lungs of 1 rabbit after three intratracheal injections at intervals of one week had similar but more extensive changes, and the lungs of another rabbit three months after a single injection had many nodules in which the alveolar spaces contained fibroplastic tissues with epithelioid cells, large vacuolated macrophages and a few foreign body giant cells (fig. 3*B*). The lungs of a rabbit seven days after an intratracheal injection of 1 cc. of glycerol had no changes.

COMMENT

Bilateral chronic exudative and indurative pneumonia developed insidiously in the lungs of a man engaged in a furniture-manufacturing business. The diffuse exudative and indurative consolidation of the lungs with only minimal deposits of fibrin on the visceral pleura resembled grossly, or at least suggested a resemblance to, the lung changes with massive aspiration of liquid petrolatum. Alcohol and ether extraction of these lung tissues demonstrated the presence in large quantities of a viscous material whose general solubility and simple chemical and physical properties approximated those of a wood-finishing substance like shellac dissolved in some oil medium. Presumably this material entered the lungs by inhalation of small particles dispersed by pressure in sprays. The particles of material gradually accumulated in the terminal bronchioles and alveolar spaces of the lungs, and the irritant properties of the material caused the chronic exudative and fibroplastic inflammation. This causal relation was tested experimentally by injecting emulsions of the shellac-like material recovered from the human lungs into the tracheas of rabbits. The lungs of these animals examined later revealed extensive exudative and fibroplastic inflammation.

Chronic inflammation of the lungs caused by lac substance and certain oil solvents is another form of a pulmonary disorder commonly designated as lipoid pneumonia. The changes in the lungs demonstrated by microscopic examination of the tissues differed from those with liquid petrolatum in that there was a much greater exudation of polymorphonuclear leukocytes and an abundant fibroplastic tissue response in the alveolar spaces and bronchioles, without the presence of many large mononuclear lipophages. In these respects the reactions were more like those reported in tissues with chaulmoogra oil. The tissue reaction observed in the human lungs and those observed experimentally in the lungs of rabbits following the intratracheal injection of the extracted laclike material were due probably to the fatty acid composition of this material. Although the composition of the pure lac resin has not been established and probably varies considerably in different preparations, at least two constituent fatty acids have been isolated: (1) aleuritic, a trihydroxypalmitic acid, comprising about 30 per cent, and (2) shellolic acid, believed by some to be a dibasic dihydroxyhydroaromatic acid, comprising about 10 per cent. The remaining 50 to 60 per cent of the resin consists of fatty acids unidentified or regarded as hydroxyacids similar to shellolic. The presence of fatty acids in tissues is known to cause necrosis and marked exudative and fibroplastic tissue reactions. Some of these tissue changes seem related to the acidity developed by the migration of hydrogen ions into the aqueous tissue medium in exchange for base ions entering the oil at the water-oil interphase.

SUMMARY

Chronic progressive induration developed in the lungs of a man engaged in manufacturing furniture. The postmortem examination demonstrated chronic diffuse exudative and indurative pneumonia in both lungs. The character of the consolidated tissues in the lungs and the small deposits of fibrin on the visceral pleura suggested grossly the possibility of some form of lipoid pneumonia. Ethyl alcohol and ether extraction of the lungs yielded large amounts of a viscid material like shellac dissolved in an oil medium. This material injected into the tracheas of rabbits caused necrosis and marked exudative and fibroplastic inflammation of the lungs. The exudative and fibroplastic tissue response approximates the changes reported in tissues with oils like chaulmoogra. Lac substances have a high content of certain fatty acids. Fatty acids of this character are known to cause necrosis and marked exudative and proliferative tissue reactions.

DIFFUSE MENINGEAL FIBROBLASTOMA OF THE BRAIN AND SPINAL CORD

A REPORT OF THREE CASES

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The three cases of diffuse meningioma to be discussed in this paper are being reported because cases of this type of meningioma are rare and because they furnish additional evidence of the fibroblastic nature of meningioma whether of the diffuse or of the nodular form.

Instances of meningioma are usually classified separately with respect to the form of the growth, nodular or diffuse. The nodular form is relatively common and stereotyped in appearance. It is usually single, compact, spheroidal, causing a castlike depression in the soft tissues adjoining it in the brain or the cord. Occasionally, multiple growths occur, but even they are separated and sharply demarcated from each other. Microscopically, nodular meningioma has a characteristic appearance which varies within a comparatively narrow range. It is made up of coarse spindle cells, resembling epithelial cells, occurring in tight whorls or in looser alveoli as the case may be. The whorls may contain deposits of collagen about the centrally placed vessels and often contain corpora amylacea or psammoma bodies. Prior to Mallory's [1] work, nodular meningioma was usually diagnosed as "dural endothelioma," although many other designations had been applied,[2] including "cylindroma," "psammoma," "epithelial meningeal cancer" and "dural epithelioma." It was usually not considered to be of the same derivation as diffuse meningioma.

Diffuse meningioma is rare and varies widely in structure. There is little in its appearance either grossly or microscopically to identify it with the local tumor. It has been variously interpreted as a specific meningioblastic structure, a fibroblastic tumor, lipoma, angioma and sarcoma. When pigmented it has been reported as melanoma, and after having undergone bony metaplasia it has been called osteoma.

The name "dural endothelioma" was used because the tumor was supposed to arise from the endothelial lining of the subdural space. Mallory [1] demonstrated fibroglia and collagen fibers in a specimen fixed in Zenker's fluid within five minutes after its removal. He restudied the embryonic development of the meninges and concluded that the layer of mesenchymal cells which goes to form the dura separates from the arachnoid to form the subdural space and that the subdural space is therefore lined on both sides by a special type of fibroblast and not by endothelium. He traced the development of the whorled tumor to endothelium-like proliferations of the arachnoid villi and identified the cells that composed the whorls as fibroblasts from their ability to form fibroglia fibrils, collagen and in some instances elastic tissue. He suggested the name "arachnoid fibroblastoma" for the tumor.

Penfield [3] agreed with Mallory's interpretation of dural endothelioma and asserted that the fibrils in this tumor are not neuroglial but are a particular form of collagen. He changed the name to "meningeal fibroblastoma." Penfield stated that he was able to stain fibroglia fibrils with more or less difficulty in a series of meningeal tumors which he had studied.

Globus [2b] took exception to Mallory's identification of the tumor by means of fibrils. He reviewed the development of the meninges in fish and fowls and developed an elaborate classification for all meningeal tumors on a "philogenetic and ontogenetic" basis. He studied 103 tumors originating in the meninges and concluded that the variation in the tumors was so great that no single type cell could be responsible. He quoted the studies on the formation of the meninges by Hallerstein, Sterzi and Gelderen to support his own views and applied them to the explanation of the diffuse meningiomatous growth. He pointed out that remnants of

From the William H. Singer Memorial Research Laboratory of the Allegheny General Hospital.

1. Mallory, F. B.: J. M. Research **41**:349, 1920.

2. (*a*) Cushing, H., and Eisenhardt, L.: Meningiomas, Springfied, Ill., Charles C Thomas, Publisher, 1938, chap. 1, p. 506. (*b*) Globus, J. H.: Arch. Neurol. & Psychiat. **38**:667, 1937.

3. Penfield, W.: Surg., Gynec. & Obst. **45**:178, 1927.

undifferentiated meninges often persist beyond embryonic life and that these mesenchymal remains are often found in other pathologic conditions, such as hydrocephalus.

Weinberger [4] collected all of the instances of the diffuse type of meningeal tumor that he was able to find and reported a very unusual case of his own. In Wienberger's case, in which the patient was an 8½ year old girl, the greater part of the surface of the frontal lobe was covered with a thin pinkish layer of tumor resembling the "icing on a cake." The dura was free from the tumor. The patient made a partial recovery after removal of the neoplasm and returned to school. In his discussion, Weinberger considered that the diffuse tumor represents a zonal rest of endomeninx and may form pia-arachnoid or pia alone. He postulated that the tumor is limited in extent to the original malformation because he failed to find evidence of eccentric growth, permeation through the meningeal layers or implantation by seeding. He expressed the belief that the tumor belongs with meningioma but preferred the term "meningiomatosis." Weinberger accepted the view of Globus that there is no parent cell theory which is acceptable for the origin of meningioma and that it is best accounted for on an embryologic basis. Other cases cited by Weinberger included those of Harbitz,[5] Arlt,[6] Bailey,[7] Bailey and Bucy,[8] Lichtenstein and Ettelson,[9] Casper [10] and Conner and Cushing.[11] Of this group the case of Arlt [6] was similar to our first case: A diffuse meningioma encased the spinal cord. In Harbitz' [5] case several large yellowish incrustations filled the sulci. The largest was in the region of the sylvian fissure and spread out over the temporal and parietal lobes and the island of Reil. The tumor was composed of loose spindle cells, and the network stained positively for collagen. Bailey's case [7] was reported as one of primary diffuse sarcomatosis in a 3 year old child. The neoplasm was located in the region of the cerebellum and the brain stem. In the case of Bailey and Bucy [8] the diffuse meningioma occurred in a 45 year old woman and covered the leptomeninges "practically everywhere," filling the sulci and following the vessels for a short distance into the cortex. Lichtenstein and Ettelson [9] reported a case in which the leptomeninges of an infant were thick and white with nodules the size of a pinhead along the vessels. Casper [10] reported 2 cases. In one there were several nodular masses over the occipital lobes and at the base of the brain; in the other a sellar meningioma was observed, with thickening of the arachnoid over the entire brain. In the case of Conner and Cushing [11] there were diffuse meningeal tumors which were not visible in the gross inspection. Microscopically the condition was true sarcomatosis (endotheliomatosis); the origin was multiple and affected the adventitial sheaths of the cortical vessels. It was located in the region of the flocculus. Brown and Kernohan [12] reported a case in which the tumor was located similarly to that in our first case. It formed a sheath surrounding the spinal cord from the first thoracic vertebra to the conus medullaris and encased the cauda equina. They called the condition meningiomatosis rather than meningioma. Cases of pigmented meningioma have been recorded by Ray and Foot [13] and Brown,[14] and the origin of the pigmented tumor has been discussed by Taft.[15] A lipoblastic form has been reported by Haverfield and Walker.[16] Russell and Sachs [17] collected 4 cases of meningeal sarcoma that metastasized to distant organs and added 4 cases of sarcoma, in 3 of which there was distant metastasis. Turner and Craig [18] reported a case of osteogenic sarcoma of meningeal origin. They explained the preserved bone as an example of heteroplasia. Turner, Craig and Kernohan [19] analyzed 370 cases of intracranial meningeal tumor and considered the tumor to be malignant in 10 per cent of them. They used the term "malignant meningioma" in preference to "meningeal sarcoma" because the latter name indicates a specific tumor with an essential origin.

4. Weinberger, L. M.: Am. J. Cancer **38**:1, 1940.
5. Harbitz, H.: Acta path. et microbiol. Scandinav. **12**:24, 1935; cited by Weinberger.[4]
6. Arlt, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:713, 1936; cited by Weinberger.[4]
7. Bailey, P.: Arch. Surg. **18**:1359, 1929.
8. Bailey, P., and Bucy, P. C.: Am. J. Cancer **15**:15, 1937.
9. Lichtenstein, B. W., and Ettelson, A.: Arch. Path. **24**:497, 1937.
10. Casper, J.: Deutsche Ztschr. f. Nervenh. **96**:85, 1927; cited by Weinberger.[4]
11. Conner, C. L., and Cushing, H.: Arch. Path. **3**: 374, 1927.
12. Brown, M. H., and Kernohan, J. W.: Arch. Path. **32**:651, 1941.
13. Ray, B. S., and Foot, N. C.: Arch. Neurol. & Psychiat. **44**:144, 1940.
14. Brown, H.: Arch. Neurol. & Psychiat. **47**:271, 1942.
15. Taft, A. E.: Arch. Path. **30**:1073, 1940.
16. Haverfield, W. T., and Walker, A. E.: Arch. Surg. **42**:371, 1941.
17. Russell, W. O., and Sachs, E.: Arch. Path. **34**: 241, 1942.
18. Turner, O. A., and Craig, W. M.: Arch. Path. **32**:103, 1941.
19. Turner, O. A.; Craig, W. M., and Kernohan, J. W.: Surgery **11**:81, 1942.

REPORT OF CASES

The first 2 of our cases have been mentioned previously [20] but have not been described in detail. The third case [21] was erroneously reported from this laboratory in 1926 as one of secondary gliomatosis of the meninges accompanying a large gliosarcoma of the brain. A recent restudy shows definitely that the meningeal tumor is a separate and distinct growth which contains nodular areas presenting a structure characteristic of the local whorled meningioma and diffuse areas of the fibroblastic type which merge gradually into each other.

CASE 1.—The patient was a white man aged 57. His occupation was that of a railroad signalman, at which job he worked until three days before his admission to the hospital. The mother died of carcinoma of the bladder; the father, of Bright's disease. The patient had had typhoid fever and gonorrhea and had lost an eye in the first world war.

He first consulted his physician twenty-two days before his death on account of numbness in the two small toes of each foot and pain between the shoulders. The sensation of numbness began in the toes and extended upward to the buttocks and sometimes to the waistline. For four days intermittent pains had been radiating to the occipital region, and these were followed by nausea and vomiting. The vomiting was projectile and relieved the pain. Sleep was disturbed by headache. The patient felt weak and had lost 10 pounds (4.5 Kg.). Six years before, he had been given a spinal adjustment for pain in the left hip. He attributed the pain in his shoulder to the severity of the manipulation.

He was fairly well developed and nourished. There were no noteworthy changes on physical examination except missed heart beats, varying from three to five per minute. The blood pressure was 130 systolic and 80 diastolic.

The Romberg test was questionably positive, with swaying to the right. There were tremors of the fingers and lips. Ataxic movements were not perceptible. The right optic disk was slightly blurred, with no elevation. The retinal vessels were not dilated. The left eye was artificial. The cranial nerves otherwise were undisturbed. The deep reflexes in the right arm and the right leg were slightly increased, with clonic movements of the right ankle jerk. The abdominal and cremasteric reflexes were absent. The plantar response was normal. Sensations of touch and pain were diminished in the saddle area of the left foot and the outer part of the right foot. Fibrillations were apparent about the deltoid muscles. There was slight atrophy in the legs.

The blood showed 5,050,000 red cells and 9,350 white cells, with neutrophils 75 per cent and lymphocytes 25 per cent. The hemoglobin was 94 per cent. The blood smear disclosed no abnormalities. The urine revealed a faint trace of albumin with hyaline casts. Bence Jones protein was not found. Chemically the blood was practically normal. The Wassermann and Kahn tests of the blood were negative. Lumbar puncture revealed clear yellowish fluid on four different occasions with pressure varying from 300 to 800 mm. of spinal fluid pressure. The cell count varied between 6 and 10 white cells per cubic millimeter. The total protein varied between 670 and 1,700 mg. per hundred cubic centimeters. The Wassermann test of the spinal fluid was negative. The colloidal gold curve was 0000000000. On roentgen examination the skull presented no abnormality. There was a slight narrowing of the anterior part of the body of the seventh dorsal vertebra with some irregularity of its anterior surface. There was a slight degree of hypertrophic lipping of the articular edges of the fourth lumbar vertebra. Electrocardiographic tracings disclosed numerous ectopic ventricular contractions and was interpreted as sinus arrhythmia.

During his stay in the hospital the patient became progressively weaker and revealed many bizarre neurologic symptoms. For several days there was marked diminution of pain sensation up to the fifth dorsal dermatome anteriorly and the third dorsal dermatome posteriorly. Several days after admission he was unable to void and required catheterization. Gradually movements of the legs became difficult, following which the deep reflexes decreased and finally were absent.

Twelve days after admission he had a period of amnesia, followed by confusion. The neck became stiff, and there was flaccid paralysis of both legs. Slight weakness of the lower left side of the face was present; the tongue deviated to the left. Sensory discrimination of pain revealed a level at the first dorsal segment of the cord at this time, and the following day a level at the tenth dorsal segment was noted. There was also diminution of the sense of heat in the left arm, the left leg and the left side of the face. Position and vibratory sensations were lost in the feet. On this day lumbar puncture revealed a clear yellow fluid with a pressure of 800 mm. At times pain sensation was felt at the first lumbar segment.

The temperature ranged between 97.8 F. and 98.4 F. for twelve days, occasionally rising in the next five days to 100 F. The last two days it rose to 105 F. The respirations were 20, occasionally increasing to 22 until the eighteenth day after admission, when they rose to 40 per minute. The pulse was slow, varying between 44 and 62 until a few days before death, when it became quite rapid. He died on the nineteenth day after admission.

The clinical diagnoses considered were: (1) diffuse cerebrospinal neuropathy, (2) tumor of the spinal cord, (3) injury of the spinal cord and (4) encephalomyelitis of virus origin.

Autopsy.—The gross changes outside the brain and the cord were unimportant. The brain weighed 1,375 Gm. The dura appeared normal. The pia was congested. The brain was soft, moist and without hemorrhage or evidence of embolism or infarction. After fixation, the pia and the arachnoid appeared thickened and grayish yellow over the pons and the medulla, with extensions of this change to the under surface of the cerebellum. The grayish membrane followed the meningeal folds into the fourth ventricle and spread over the choroid plexus, where it almost completely filled the space. On cross sections the tumor was observed to surround the infundibulum of the pituitary gland and to form a thin coat about the epiphysis. It did not appear in either of the lateral ventricles. As it reached the pons it spread out in a thin layer which converged to include the medulla and the cord, which it completely surrounded. Below the medulla it consisted of a membrane of variable thickness which

20. Haythorn, S. R.; Shapera, W., and Stewart, H. C.: Am. J. Path. **18**:739, 1942.

21. Brannon, D.: Am. J. Path. **2**:123, 1926.

encased the cord throughout its length and covered it continuously like a stocking. In the region of the cauda it divided into fibrillary branches and followed the sheaths of the nerves. The amount of distortion and compression of the cord at any level varied with the thickness of the tumor.

Microscopic Description.—The extent of the tumor was confirmed microscopically. A section taken from the region of the infundibulum marked the superior point at which tumor tissue was found. Another section, which included the medulla, adjoining portions of the cerebellum of each side and the choroid plexus of the fourth ventricle, showed extensive neoplastic involvement. The meninges about the medulla were greatly thickened and replaced with tumor cells. The connective tissue of the velum interpositum was infiltrated with tumor cells, which grew in all directions and invaded the strands of that membrane. Tumor tissue displaced and compressed the choroid plexus and the connective tissue supporting its vascular portions.

The cervical cord was greatly distorted by a growth of the meninges which completely surrounded it and extended along the sheaths of the spinal nerves at their roots.

The tumor was made up of diffusely spread small spindle and round cells which had little cytoplasm. Many of the nuclei were pyknotic, although actual mitotic figures were comparatively rare. The tumor cells were generally arranged in nests or alveoli separated by a network of small vessels with lumens about the size of capillaries and walls that were thickened and hyalinized. The cells were arranged on a fine reticulum. The separating trabeculae were made up of collagen, and there were bands of collagen about vessels. While the tumor in general replaced the arachnoid layer, there were areas in which it was separated from the white columns by the collagenous pia. In other places the pia was raised from the cord and had a layer of tumor beneath it. In still other places the pia-arachnoid was entirely replaced by tumor, so that the layers were not discernible.

Not only was the spinal cord compressed and distorted by the tumor but there were places in which the tumor actually extended into the gray matter and separated the medullary sheaths. The median raphe of the cord was completely infiltrated by it. There were degenerated areas in the lateral columns in which the myelin had disappeared and the neuraxons were swollen to several times their ordinary diameters. The ganglion cells appeared degenerated, and many of them were without nuclei.

Sections from various levels of the cord showed considerable variation in the thickness of the tumor enveloping the cord. In parts of the thoracic region the tumor was thicker than the cord itself.

Numerous stains were applied to demonstrate fibroglia fibrils, collagen, reticulum, myelin and fat. There were no fat cells in the growth. Myelin was not present except about the nerve trunks which passed through the growth. The tumor produced fibroglia, collagen and a fine argentophil reticulum which proved its fibroblastic derivation. Since it grew rapidly and invaded other tissues, it was considered sarcomatous.

The anterior lobe of the pituitary gland was compressed and smaller than usual. A part of the posterior lobe was invaded by direct extension of the tumor growth.

The pathologic diagnosis was rapidly growing diffuse meningeal fibroblastoma or meningeal sarcoma.

CASE 2.—The patient was a white man aged 31, married, a lithographer. He was a moderate user of tobacco, alcoholic liquors and coffee. His chief complaint was headache, which began two weeks before admission, at the time a cold was contracted, and persisted until death. On the morning of admission he awoke with severe frontal headache, which later spread toward the occiput.

He was a well developed, well nourished man, lying in bed in a semistuporous condition. He was able to answer questions but raised his eyelids with difficulty. The general physical examination gave negative results. The blood pressure was 126 systolic and 70 diastolic.

There was no nuchal rigidity. There were questionable Kernig signs bilaterally. The deep reflexes were equally present. The abdominal reflexes were decreased on the right side, and the Babinski reflex was equivocal bilaterally. Ophthalmoscopic examination revealed pale and somewhat blurred disks. The cranial nerves were otherwise undisturbed. Sensations were intact. There was no motor weakness.

The patient's headache increased and he became drowsy. He vomited brown fluid. Spinal puncture showed a fluid pressure of 150 mm. All specimens were tinged with blood. The following day the blood pressure increased to 134 systolic and 80 diastolic. The pulse was 56. The patient became delirious, and ptosis of the left upper eyelid and twitching of the left arm developed. The optic disks became elevated. The general condition became gradually worse and death occurred three and a half hours after the development of the twitching of the arm.

The clinical diagnosis was spontaneous subarachnoid hemorrhage.

Autopsy.—The brain weighed 1,400 Gm. The meninges were much congested. As the frontal lobes were lifted from the floor of the skull, a huge mass of clotted blood, which weighed 150 Gm., was found beneath the left frontal lobe. The clot was adherent to the dura over the supraorbital plate and was stripped from the under surface of the left frontal lobe with little difficulty. The under surface in the region of the second and third inferior gyri was softened to a mushy consistency, and the convolutions were compressed. The floor of the anterior horn of the left lateral ventricle was very thin and at one point measured 0.5 cm. in thickness. After the brain was hardened, a zone of encephalomalacia was found which involved the inferior frontal gyrus. At the apex of the softened area was a small vessel filled with clot. The brain tissue about it contained small hemorrhages and presented a honeycomb appearance. This zone was in close relation to the clot which filled the arachnoid space. Cross sections were made at centimeter intervals and the softened area found to extend backward to a point just beneath the floor of the lateral ventricle. The clot contained whitish strands, but tumor was not suspected in the gross examination.

Microscopic Description.—Sections were taken from the dura and the arachnoid over the supraorbital space, beneath the hemorrhage described in the gross specimen. The arachnoid was thrown into numerous folds, attached to which was a rapidly growing malignant tumor. Parts of the tumor had undergone necrosis and were infused with blood from the hemorrhagic zones. In the perivascular zones the tumor was very cellular and was made up of round, oval and spindle-shaped cells with large vacuolated nuclei and prominent nucleoli. In places the cell polarity was lost. Many cells were pyknotic, and many of them showed mitotic figures. Special stains were made of this section. The phosphotungstic acid–hematoxylin stain failed to show the presence of fibroglia or neuroglia fibrils, possibly because

the mass was fixed in a solution of formaldehyde. Masson's stain showed that portions of the growth were permeated by strands of collagen which appeared to be continuous with the collagen about the vessels and dura. Silver stains showed fine reticulum permeating the entire tumor.

Some of the sections taken from what appeared to be clot in the gross specimen showed that it was made up of both tumor cells and blood clot. The cells in these sections were multinucleated and showed many mitotic figures and much pyknosis. There were large zones in which the cells were spindle shaped and resembled the structure of a spindle cell sarcoma.

Several sections were taken from the region of the first and second frontal gyri immediately above the hemorrhage. Where the meninges remained intact, there was an extensive subpial hemorrhage with areas of softening involving the white matter.

The brain was edematous, and the Virchow-Robin spaces were widely distended with fluid. Two sections from the brain showed thrombosed vessels with a wedge-shaped hemorrhage involving the white matter beneath the meninges. The pia-arachnoid appeared to be broken at one point. Two large sections showed the presence of thrombi in the cerebral vessels with diffuse bleeding into the meninges and into the adjoining brain tissue. In the neighborhood of the hemorrhagic areas the brain showed zones of recent encephalomalacia. One of the veins in the meninges immediately beneath the softened area showed active phlebitis with permeation of its wall by segmented leukocytes and mononuclears. The cerebellum appeared normal.

The pathologic diagnosis was meningeal sarcoma with large subdural clot and localized encephalomalacia.

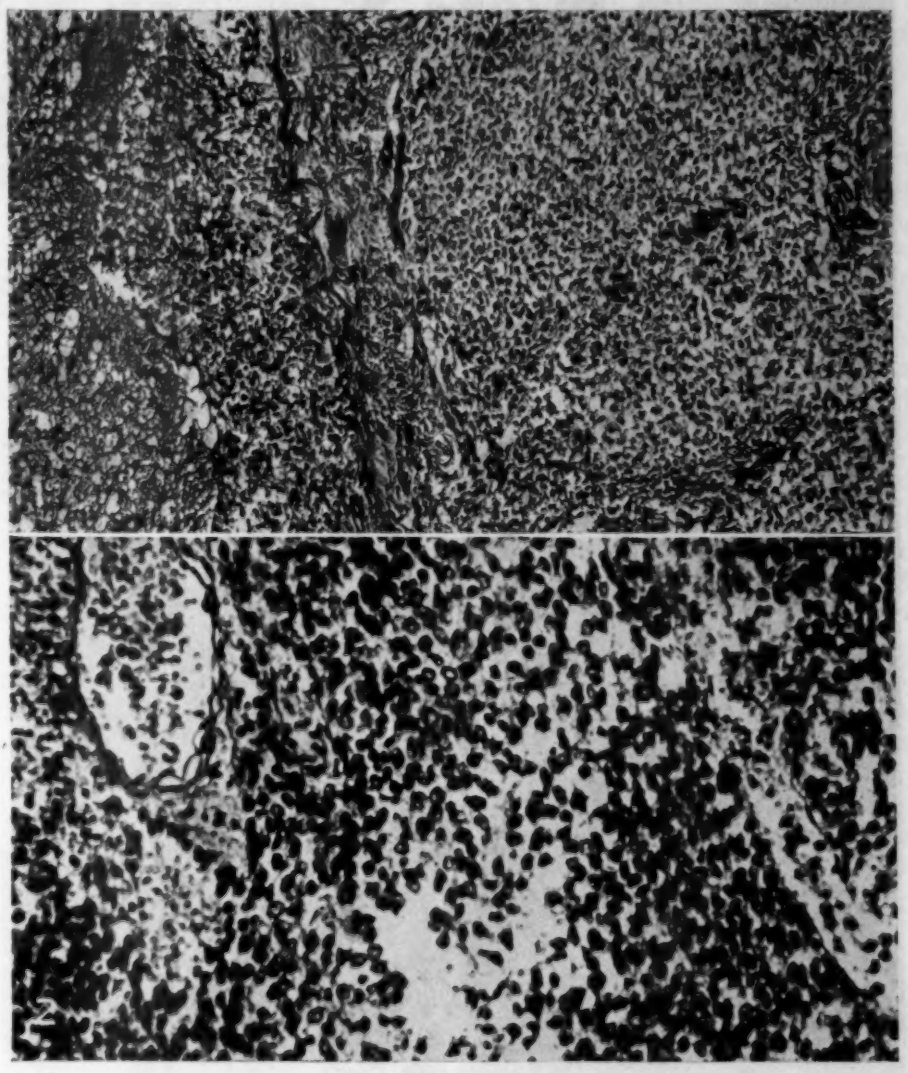

Fig. 1 (case 1).—Meningeal sarcoma of the spinal cord; × 90. At the extreme left some of the white matter of the lateral columns is seen. Adjoining the cord on the right is a portion of the growth beneath the pia. The wide collagenous band crossing from above downward is pia. At the right of it the diffuse tumor is again seen.

Fig. 2. (case 2).—Meningeal sarcoma; × 280. The photomicrograph shows the cellular nature of the growth, the absence of stroma and the thin-walled vessels.

The third case, already described in the literature under the title of "Secondary Gliomatosis of the Meninges," [21] largely because it occurred in the same brain with another tumor, has been

restudied, and we are convinced that the meningeal part of the tumor is meningioma and is worthy of reconsideration because it indicates that the division of meningioma into diffuse and nodular types is a superficial one. In this case both diffuse and nodular forms were present together, and one form shaded gradually into the other. The type cell was the same for both.

Case 3.—A white girl 13 years old died following a craniotomy for relief of pressure. The complete history may be found in the published report.[21]

Autopsy.—The weight of the brain was 1,115 Gm. Briefly, there was a "large, firm tumor which projected from the left basal ganglia, well to the right of the midline and displaced the right basal ganglia." It involved the upper portions of the optic thalamus and was 4 to 5 cm. long and 3 cm. wide.

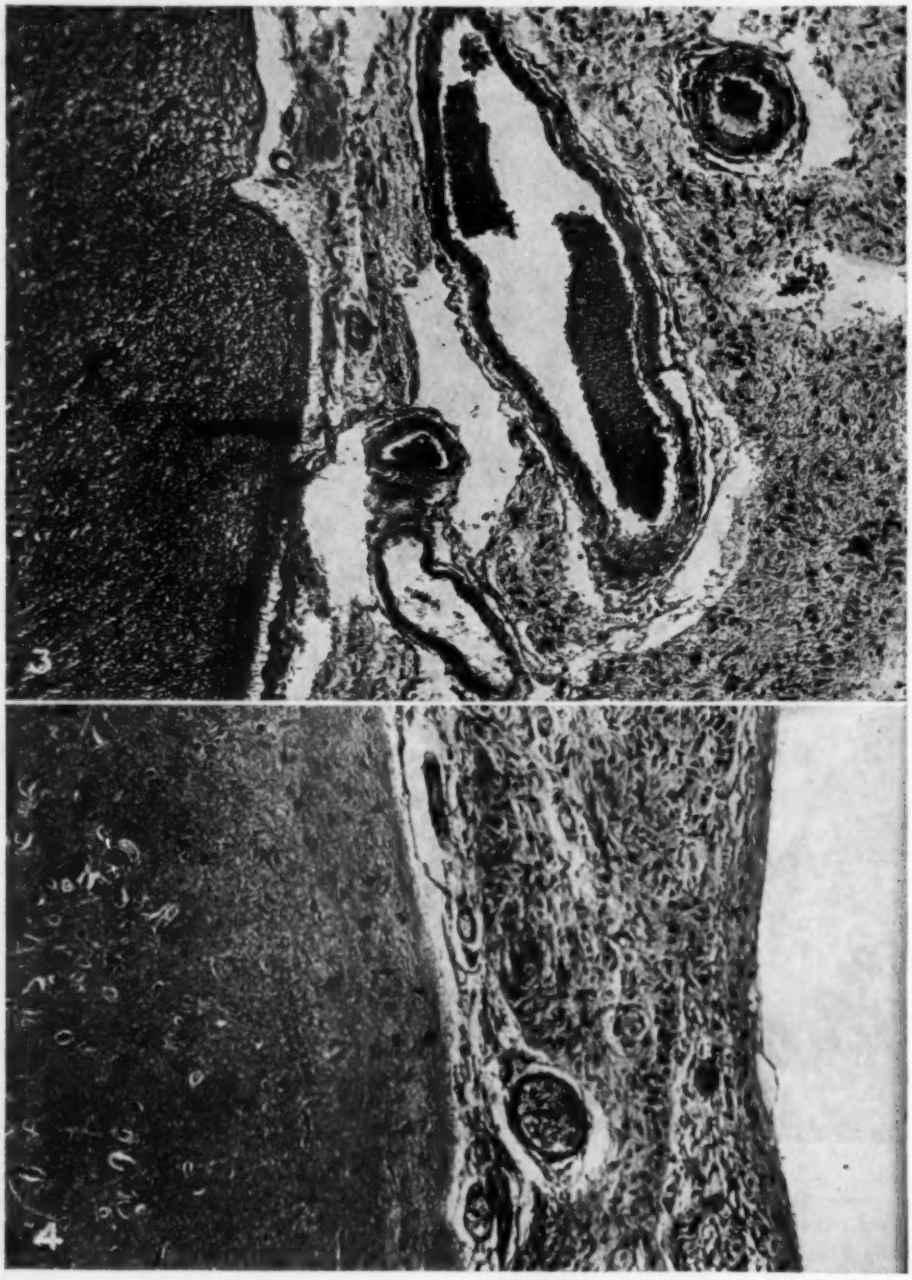

Fig. 3 (case 3).—Meningeal fibroblastoma of the pia-arachnoid; × 90. The growth involved the pia-arachnoid and was not found beneath the pia. The portion of the tumor shown in this photomicrograph was made up of fibroblastic elements arranged in a diffuse and loosely woven manner, and there was no evidence of rapid growth.

Fig. 4 (case 3).—Meningeal fibroblastoma of the pia-arachnoid; × 90. The section was taken from another portion of the same tumor as that shown in figure 3. In this section the tumor is growing in the compact nodular form with quite definite whorls.

The meninges at the base of the brain resembled the exudate of chronic meningitis. The leptomeninges were dull and opaque. The subarachnoid space and the cisterna were filled with what was taken to be a thick exudate but which proved on microscopic examination to be tumor. The material obscured the basal vessels, the optic chiasm and the exits of the cranial nerves. It extended over the lateral and anterior aspects of the temporal lobes, the base of the cerebellum, the pons and the medulla.

Microscopically, the tumor of the basal ganglions consisted of the main mass, which was diagnosed as gliosarcoma, and a smaller nodule lying within it that was not diagnosed. Glial fibrils were not observed in either of the brain tumors with Mallory's phosphotungstic acid–hematoxylin stain. The larger mass invaded the choroid plexus, where there was no question of its secondary nature.

The growth of the pia-arachnoid over the brain stem and basilar regions, which was believed to be meningitis in the gross inspection, was made up of spindle cells arranged in the form of a diffuse membrane. It did not invade the brain from which it was excluded by the pia, but formed a fibrillar network in the arachnoid. The fibrillar network was taken to be a form of gliosis extending from the gliosarcoma although no point of connection between the tumor of the brain and the arachnoid could be found. The report states that in some portions it "somewhat resembled an endothelioma of the meninges." Phosphotungstic acid–hematoxylin staining of the meningeal tumor showed beautiful fibrils, believed at the time of the report to be glial, and coarse brown fibers suggestive of collagen.

In the restudy of the case there is nothing to add to the report itself, but in the light of the newer classification of tumors of the brain by Bailey and Cushing [22] and by others we have changed the diagnosis and now interpret the case as one of two unrelated intracranial tumors. We think that the large tumor of the brain would now be called "glioblastoma multiforme" and the smaller inclusion within it an isolated nodule of bipolar spongioblasts. We feel sure that the meningeal tumor is meningeal fibroblastoma and has both diffuse fibrillar and compact nodular portions.

Our reasons for these conclusions are: 1. The tumor of the brain and the meningeal tumor were cytologically different. 2. Where the tumor of the brain invaded the ependyma and the choroid plexus, its original structure was repeated and typical glial giant cells were formed. The meningeal tumor did not repeat the structure of the principal growth and did not contain giant cells. 3. The meningeal tumor was confined to the pia-arachnoid, and there was no connection between the two tumors. 4. Fibrils were not shown in the tumor of the brain but were abundant in the meningioma. While neuroglia and fibroglia fibrils stain alike with Mallory's phosphotungstic acid–hematoxylin stain, the arrangement in this case was that of fibroglia. 5. There are several instances in the literature of tumor of the brain and unrelated meningioma having occurred in the same case (Cushing and Eisenhardt [22a]; Courville [23]). Courville reviewed and tabulated 134 cases of multiple intracranial tumors and stated that almost every combination of multiple intracranial tumors occurs from the standpoint of location, tissue, origin and degree of malignancy.

22. Bailey, P., and Cushing, H.: Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926.

SUMMARY AND COMMENT

In 2 of the 3 cases of diffuse meningioma reported the neoplasm was invasive and showed other evidences of rapid growth, such as multiple mitoses. In the third case the growth was both diffuse and nodular. In all 3 cases the tumor involved the pia-arachnoid. In the first case it grew on both sides of the pia, and in the second it was attached to the dura and separated from the brain by the pia. In the first and third cases the tumor showed fibroglia fibrils with Zenker's fixation and Mallory's phosphotungstic acid–hematoxylin stain. In the second the tumor was fixed in a solution of formaldehyde, which does not preserve fibroglia fibrils. The demonstration of fibroglia fibrils and collagen fibers identified the tumor cell as a fibroblast. Fibroblasts are polypotential cells, capable of forming diffuse membranes, nodular structures, chondromucin, cartilage and bone, and may take up fat. Special types of connective tissue cells of the meninges may be pigmented (Taft [15]). The rapid course in the first case argues in favor of tumor (meningioma) instead of an embryonic mesenchymal rest as postulated by Globus.[23b] In all 3 cases the growth appeared to be a true neoplasm of fibroblastic origin and in our opinion should be classed as meningeal fibroblastoma rather than "meningiomatosis." Apparently meningiomatosis would be hyperplasia of meningeal elements, although we were unable to find the word in either of the most recent editions of two standard medical dictionaries.

In the first 2 cases the tumor was a fibroblastic cancerous growth, and we believe it should be called either "meningeal fibroblastoma" or "meningeal sarcoma," since substituting the term "malignant meningioma" makes a distinction without a difference. Finally, the third case ties up diffuse and nodular meningioma as variations of one and the same cytologic entity.

23. Courville, C. B.: Am. J. Cancer **26**:703, 1936.

MORPHOLOGIC STUDIES OF RATS DEPRIVED OF ESSENTIAL AMINO ACIDS: I. PHENYLALANINE

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DETROIT

It is widely known that certain amino acids are necessary for growth and the maintenance of health,[1] but there are few studies pertaining to the effects of specific amino acid deficiencies on particular organs or tissues. Numerous investigations have shown that animals fail to grow normally if placed on diets deficient in essential amino acids. It has also been shown that in both human and animal populations fertility decreases following periods of poor nutrition[2]; when rats were placed on diets deficient only in tryptophan,[3] the animals failed to respond.

Indirect evidence of the anatomic alterations associated with deficiencies in amino acids has been presented by studies on choline metabolism.[4] In rats consuming low choline diets the liver became fatty and necrosis of the tubular epithelium of the kidneys developed; these changes were augmented by the addition of cystine and were alleviated by the addition of methionine. Recently more complete anatomic studies have been reported by Harris and his co-workers,[5] who placed rats on synthetic diets almost completely free of lysine. In the six weeks of the experimental period the animals on the deficient diets ceased to grow while those of the control group developed normally. Postmortem examination of the animals of the deficient group showed a general wasting of soft tissue, while blood studies revealed hypoproteinemia and a decrease in hemoglobin as well as in red blood cells. Roentgenograms of bones showed decreased calcification, and prepared sections of long bones revealed narrowed epiphyses. The testes of the deficient animals were smaller by volume and showed fewer mitoses. The foregoing alterations, in the opinion of Harris and his co-workers, followed an inability of the animals to form adequate proteins. They believe that the changes are comparable to those seen in starvation.

In view of the paucity of information available to biochemists and morphologists it seemed desirable to gather data regarding the anatomic changes that occur in animals completely deficient in only one essential amino acid. In each experiment we have selected a group of young rats of a single strain, of the same age and of comparable weight. The diet of the deficient rats was similar to that of a control group except that in each experiment it was deficient in a single amino acid. In the first experiment, recorded here, the animals were deprived of phenylalanine.

EXPERIMENTAL PROCEDURE

Animals.—Weanling rats of the Sprague-Dawley strain, 25 to 28 days old, were employed in our experiment. Ten control animals were fed a complete synthetic diet containing a mixture of essential amino acids as the source of nitrogen, and 10 experimental animals were fed a diet similar in all respects except that phenylalanine was omitted. The paired feeding technic was employed. Each animal was kept in an individual cage designed to prevent coprophagy.

Diets.—Both the control and the deficient diet consisted of salt mixture (Wesson[6]) 4 per cent, celluflour 2 per cent, sucrose 67.25 per cent, halibut oil 0.4 per cent, corn oil 3 per cent, and amino acids 23.35 per cent. The amino acid mixture[7] contained l-lysine[8]

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1. Albanese, A. A.; Holt, L. E., Jr.; Kajdi, C. N., and Frankston, J. E.: J. Biol. Chem. **148**:299, 1943.

2. Allen, E.: Sex and Internal Secretions, ed. 2, Baltimore, Williams & Wilkins Company, 1939, chap. 22.

3. Albanese, A. A.; Randall, R. M., and Holt, L. E., Jr.: Science **97**:312, 1943.

4. Griffith, W. H., and Wade, N. J.: J. Biol. Chem. **132**:627, 1940.

5. Harris, H. A.; Neuberger, A., and Sanger, F.: Biochem. J. **37**:508, 1943.

6. Wesson, L. G.: Science **75**:339, 1932.

7. Frederick Stearns & Company supplied all the amino acids and vitamins required in these experiments.

8. This amino acid was administered in the form of a monohydrochloride.

16 Gm., dl-tryptophan 3.2 Gm., l-leucine 12.8 Gm., dl-isoleucine 16 Gm., dl-valine 22.4 Gm., dl-methionine 9.6 Gm., l-arginine[8] 3.2 Gm., l-histidine[8] 6.4 Gm. and dl-threonine 16 Gm. per 500 Gm. of diet. The control diet contained in addition 11.2 Gm. of phenylalanine. In the phenylalanine-deficient experimental diet the aforementioned amount of phenylalanine was replaced isocalorically by sucrose. The diets were supplemented with 4 mg. of thiamine hydrochloride, 8 mg. of riboflavin, 4 mg. of pyridoxine hydrochloride, 4 mg. of nicotinic acid, 20 mg. of calcium pantothenate, 600 mg. of paraaminobenzoic acid, 50 mg. of alpha tocopherol, 2 Gm. of inositol and 2 Gm. of choline hydrochloride per kilogram. The average daily food intake was 2.53 Gm.

Duration of Experiment.—The rats were maintained on the respective diets for twenty-eight days. Two deficient rats died several hours before they were to be killed (experiments 4 and 5).

At the termination of the experimental period the animals were killed by decapitation without anesthesia, since this procedure provided blood in sufficient quantities. From 1.0 to 1.5 cc. was collected in an evaporating dish containing sodium oxalate. The amount of spinal fluid was negligible, as shown by an analysis made and compared with an analysis of blood from the abdominal portion of the aorta. After removal of samples for hemoglobin determinations, the remainder of the blood was centrifuged and determinations of plasma proteins carried out on the plasma.

Autopsies.—Autopsies were made immediately following the death of the animals. Each organ was inspected and routinely weighed. The entire organs or sections of them were fixed in 4 per cent solution of formaldehyde. One each of the paired organs, as well as sections of the liver and the kidney, were fixed in Zenker's fluid. Sections of the sternum, the vertebrae and the long bones were decalcified in Zenker's fluid. The tissues were embedded in paraffin, sectioned and stained routinely with hematoxylin and eosin. Additional stains were employed as necessity demanded. Each eye was fixed in Zenker's fluid, one of them was embedded in paraffin, and the other in celloidin.

RESULTS

Health of the Deficient Animals.—The animals on the phenylalanine-deficient diets appeared to become progressively weaker throughout the experimental period. These rats were inactive and reacted slowly to stimuli. Their hair appeared coarse and unkempt. At the completion of the experimental period they were obviously smaller than the control rats, and their extreme weakness made it difficult for them to walk. Two animals (rats 4 and 5) died several hours prior to the time at which they were to be killed.

Changes in Weight.—Although the amount of food consumed by the deficient and the control animals was the same (average, 2.53 Gm. per day), the rats on the deficient diet did not maintain their weight; all showed a significantly greater loss in weight (average, 16 Gm.) than did the control animals (average, 4.75 Gm.).

Organ Weights.—Each organ was weighed immediately after its removal, and the percentage of organ weight was determined. The percentage of organ weight equals $\frac{\text{organ weight}}{\text{body weight}}$. The weights were compared in each experiment, and the totals were submitted to statistical analysis. The most pronounced variation was noted in the thymuses. The glands of the deficient animals

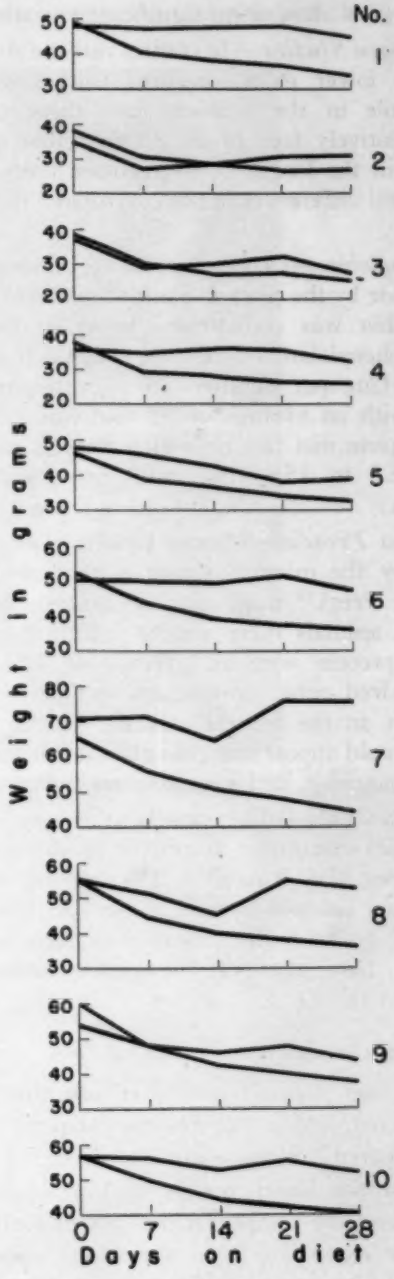

Fig. 1.—Comparison of the weight curves of each pair of rats, one deficient in phenylalanine, the other a control. The deficient animals weighed the least at end of experimental period.

proved to be markedly atrophic, the mean being 21.2 ± 2.9 mg., compared with 54.5 ± 7.6 mg. for the control animals. The average organ weight of the deficient animals proved to be 0.115 per

cent, compared with 0.183 per cent for the control animals. The testes of the deficient rats proved to be uniformly smaller than those of the control group, the mean weight being 95 ± 7.6 mg. for the deficient animals and 278 ± 70 mg. for the control animals. The weights of the other organs showed no significant variations.

Roentgen Studies.—In control rats the stomach and the lower gastrointestinal tract contained gas, while in the deficient rats these organs were relatively free of air. Other than a difference in the length of long bones, there were no skeletal differences in the control and deficient groups.

Hemoglobin.—Determinations of hemoglobin were made by the Sheard-Sanford method.[9] The hemoglobin was consistently lower in animals on the phenylalanine-free diet, ranging from 7.4 to 14.0 Gm. per hundred cubic centimeters of blood, with an average of 9.9 Gm.; animals on the complete diet had hemoglobin levels ranging from 13.7 to 15.8 Gm., with an average of 14.7 Gm.

Plasma Protein.—Plasma protein was determined by the micro-Kjeldahl method with the aid of a Pregl[10] distillation apparatus. In the deficient animals there was a reduction of the plasma protein with an average of 4.71 Gm. per hundred cubic centimeters, compared with 5.58 Gm. in the control animals. From these data it would appear that phenylalanine influences both hemoglobin and plasma protein formation.

Hepatic Fats.—The fats of the liver were determined essentially according to the method of Leathes and Raper.[11] The hepatic fat of the control animals proved to be 4.56 Gm. per hundred grams, which was not significantly different than that of the deficient animals (3.97 Gm.).

MORPHOLOGIC OBSERVATIONS

Heart and Blood Vessels.—The entire heart was bisected, and sections of the complete organ were prepared. Sections obtained from the aorta and from the blood vessels of the lungs, the kidneys and the peripheral muscles of each animal were examined. No alterations were observed in the cardiac muscle, and the blood vessel walls of the deficient animals appeared to be comparable with those of the controls.

Lungs.—Complete sections of both lungs were examined. The lungs of both the control and the deficient animals proved to be normal save for the lungs of 2 deficient rats that died on the day they were to be killed. Nodular masses in these lungs were noted on the gross specimens, masses that on histologic examination proved to be focal areas of bronchopneumonia.

Liver.—The livers of the two groups of animals were comparable and presented no abnormalties.

Spleen.—The spleens of the two groups presented no gross abnormalities, but those of the deficient animals showed congestion of the pulp. The structure and the cells appeared normal.

Kidneys.—On gross inspection the kidneys of both deficient and control animals appeared normal and comparable in size. However, the kidneys of the deficient animals were somewhat increased in weight. Inspection of the glomeruli and tubules and the vessels revealed no alterations in either the deficient or the control group.

Urinary Bladder.—The urinary bladders of both the control and the deficient animals were normal.

Gastrointestinal Tract.—On gross inspection the gastrointestinal tracts of both groups of animals appeared to be normal. Sections were obtained from both portions of the stomach, from three levels of the small bowel and from the several levels of the large bowel. The mucosa was well preserved in all animals and showed no histologic alterations.

Skin.—The hair of the deficient animals was stringy and coarse to palpation. Inspection of the skin showed an increased amount of subcutaneous fat and connective tissue in the control group. Examination of the prepared sections taken from the ventral and lateral abdominal walls showed the epidermis and the corium to be comparable in the two groups. Although no detailed studies were made, there were no obvious differences in the appearance of the hair follicles.

Voluntary Muscle.—The muscles of the deficient group of animals appeared similar to those of the control animals, although they were somewhat smaller. Histologic study of the muscles revealed no alterations in either group.

Bones and Joints; Marrow.—Examination of longitudinal sections of the tibia and the femur, softened in Zenker's fluid, revealed these facts: 1. The epiphysial cartilages of the deficient rats were consistently narrower than those of the control animals. To check this observation the

9. Sheard, C., and Sanford, A. H.: J. Lab. & Clin. Med. **14**:558, 1929.

10. Pregl, F.: Die quantitative organische Mikroanalyze, ed. 2, Berlin, Julius Springer, 1912.

11. Leathes, J. B., and Raper, H. S.: The Fats, ed. 2, New York, Longmans, Green & Co., 1925.

width of the cartilage disk was measured at three zones. The average width of the disk for the 10 deficient rats proved to be 0.116 mm., compared with an average of 0.174 mm. for the control animals. The cartilage cells in the deficient rats showed no alterations, but the columns of cells in the control group were more uniformly arranged. This alteration along with the presence of islands of cartilage encircled by bony trabeculae on the joint margins of the cartilage produced some irregularity of the epiphysial line in the deficient animals. 2. The bony trabeculae appeared more prominent and larger in the control animals. This difference was not striking, and the degree of calcification appeared equal in both groups.

Marrow was available for examination from the long bones, the sternum and the vertebrae. There were no alterations in the marrow specimens of either group.

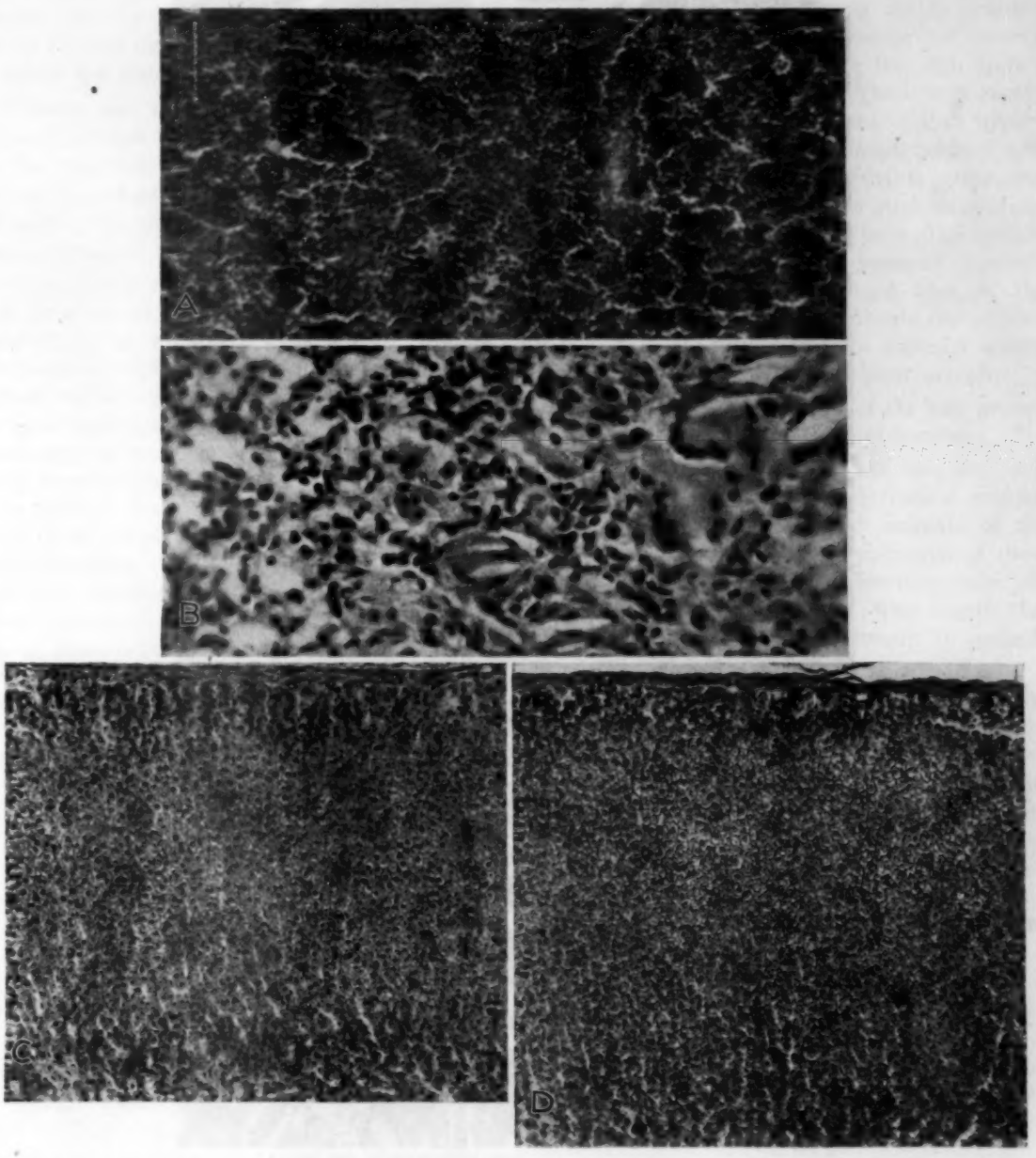

Fig. 2.—*A*, thymus from the control animal of pair 1; *B*, thymus from the deficient animal of pair 1. Hematoxylin and eosin; × 80. *C*, adrenal gland from the control animal of pair 7; *D*, adrenal gland from the deficient animal of pair 7. Hematoxylin and eosin; × 150.

Brain, Spinal Cord and Nerves.—In each instance the fixed brain was sectioned so that the

entire organ was available for study. Sections of the spinal cord were taken from at least three levels, and peripheral nerves were studied in muscles taken from the legs. No alterations were observed in the central or the peripheral nervous system of any of the normal or the deficient rats.

Eyes.—Neither the eyes of the deficient nor those of the control animals showed alterations.

Pituitary Gland.—In an attempt to preserve the pituitary gland intact the base of the skull and the attached pituitary gland were fixed in Zenker's fluid. Unfortunately, it was difficult to prepare sections of the gland with this preparation; so only four glands from the deficient and control groups were available for examination. The sections were cut at 4 microns and stained with hematoxylin and eosin and with

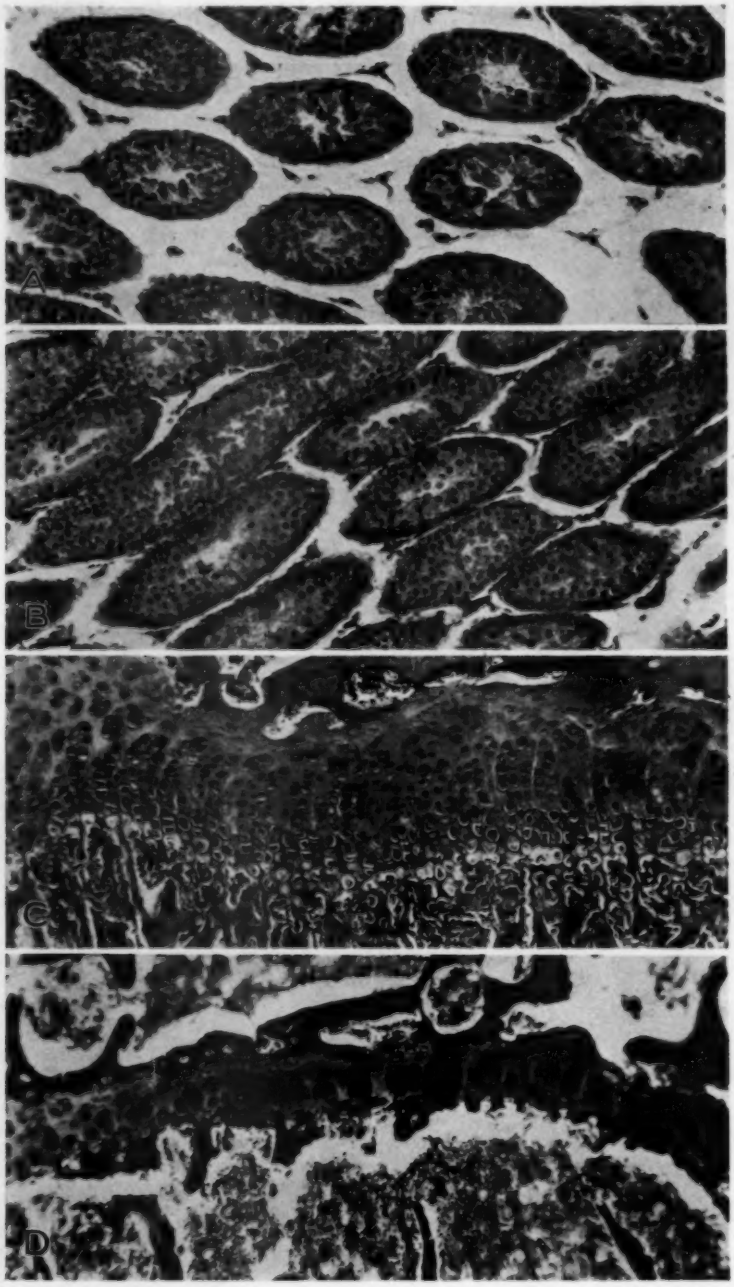

Fig. 3.—*A*, testis from the control animal of pair 2; *B*, testis from the deficient animal of pair 2. Note sloughing of the epithelium in the lumens. Hematoxylin and eosin; × 150. *C*, section of a femur of the control animal of pair 5; *D*, section of a femur of the deficient animal of pair 5. Hematoxylin and eosin; × 80.

azocarmine. No alterations were noted in either the deficient or the control group.

Thyroid and Parathyroid Glands.—Because the animals were decapitated, it was difficult to find the thyroid gland. However, by preparing numerous sections from the soft tissues of the neck the gland was found in 2 rats of the deficient group and in 3 rats of the control group. In all a parathyroid gland was embedded in the thyroid tissue. No differences were noted between the glands of the two groups.

Thymus and Lymph Nodes.—At autopsy the thymus of each of the deficient rats was found to be extremely small and in some instances almost impossible to identify, while the thymus of each of the control animals filled the superior mediastinum.

Examination of the prepared sections showed the structure of the thymuses from the control animals to be well preserved and the cellular elements normal. The obvious atrophy of the glands of the deficient animals was more striking on histologic study. The atrophy varied from moderate to severe, so that in some instances only remnants of the gland could be identified. The earliest changes were represented by thinning of the lymphoid elements of the cortical zone with resultant narrowing. As these lymphoid elements became more sparse, the connective tissue stroma and the reticulum became relatively more prominent. In those glands presenting severe atrophy, only a few lymphocytes were scattered through a thin cortex, while the medullary regions formed the bulk of the organ. In addition to the apparent relative increase in stroma, proliferation of the reticular cells was observed, and numerous giant cells were noted in mature and apparently newly formed stroma. The central portions of such lesions contained numerous irregular clefts typical of cholesterol deposits. The giant cells were often of the foreign body but more frequently of the Langhans type. The formed granulomas were most prominent in the glands that were markedly atrophic; only a few giant cells could be found in the more normal glands.

Lymph nodes were obtained from the axilla, the mediastinum and the neck. The structure of all was well preserved, and no abnormalities were found in the nodes removed from either the control or the deficient groups of animals.

Adrenal Glands.—Although the adrenal glands from both groups of animals were on gross examination almost equal in weight, histologic study revealed noticeable changes in the glands of the deficient rats. These alterations varied with each animal and were observed only in the cortex. It was apparent by examination under low magnification that the structure was usually well preserved but that thinning of the cortex was often present. The intermediate zone almost uniformly appeared to be crowded or compressed as compared with that of the control animal. In addition, numerous nuclei of the cells of the intermediate zone appeared as deeply stained dense granular masses. More careful inspection of these nuclei disclosed a few thin spirals and often chromatin clumps. These may represent atypical or abortive mitoses. Other hypertrophied nuclei showed prominent nucleoli and large masses of chromatin. Further inspection of the intermediate zone under high magnification showed the cells to be smaller and to contain less lipoid. The intervening vascular channels were more prominent here and also in the reticular zone. In deficient animals the cellular compression and the prominent vascular spaces were probably produced by cellular atrophy.

Pancreas.—The pancreases of the two groups of animals were comparable and normal.

Female Genital System.—The ovaries, oviducts and uteri were available from 3 animals of the deficient group and 3 animals of the control group. Admittedly, evaluation of these tissues is difficult, but no differences were observed in either group. It was noted that maturation of follicles was present in animals of the deficient group.

Male Genital System.—Testicular atrophy was prominent in most animals maintained on the phenylalanine-deficient diets. Examination of the prepared slides presented more striking changes. The tubules of the testes of the deficient animals appeared smaller, and the cellular alterations were prominent. Large eosinophilic-staining cells and considerable cellular detritus were found in the lumens of the atrophic tubules. Few cells had developed beyond the stage of the primary spermatocytes, and the Sertoli cells were prominent. The interstitial cells and the cells of the epididymis showed no prominent alterations. Unfortunately, the prostate gland and seminal vesicles were not removed for examination.

COMMENT

Some of the anatomic alterations observed in phenylalanine-deficient rats have previously been observed in experiments on chronic and general malnutrition.[12] It has been observed that under-

12. Jackson, C. M.: The Effects of Inanition and Malnutrition upon Growth and Structure, Philadelphia, P. Blakiston's Son & Co., 1925.

fed rats show a retardation of skeletal growth and that rats fed on lysine-deficient [8] diets have narrowed epiphyses and a decrease of calcium in their bones, the latter not observed in these studies, however. Profound thymic atrophy has been frequently noted in both man and animals following acute and chronic inanition, and the decrease observed in the lymphoid portions of the gland apparently simulates the atrophy noted here in phenylalanine-deficient rats. Atrophy of the adrenal cortex [13] with a decrease in the lipoid content of the cortical cells has also been noted, differing little from that observed in the present experiment. Retrogressive alteration in the epithelial cells of the seminiferous tubules in the phenylalanine-deficient rats and in those reported on starvation diets is less severe than the alteration in vitamin E [14] deficiency but about equal to that in vitamin A deficiency.

13. Jackson, C. M.: Am. J. Anat. **25**:221, 1919.
14. Mason, K. E.: Am. J. Anat. **52**:153, 1933.

SUMMARY

Young rats were fed synthetic diets of crystalline amino acids, crystalline vitamins, fats and dextrin plus the necessary salts. The animals were pair fed so that the rat of the control group received the exact quantity of food that his previously fed paired partner of the deficient group received. The control animals received a balanced diet while those of the deficient group received a diet devoid of phenylalanine but otherwise identical with the control diet. During the experimental period of twenty-eight days the animals of the deficient group lost weight, gradually became weaker and in general appeared unkempt.

Those rats fed on diets deficient in phenylalanine showed these results: a reduction in hemoglobin and plasma proteins; narrowing of the epiphysial cartilages of the long bones; marked atrophy of the thymus; atrophy and decreased lipoid content of the adrenal cortex; degeneration and atrophy of the seminiferous tubules of the testes.

PATHOLOGY OF ANAPHYLAXIS DUE TO SULFONAMIDE DRUGS

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Systematic study of the pathology of human anaphylaxis is in its infancy. Most of the recognized instances of anaphylactic death are of the sudden, dramatic variety, with no time for the appearance of morphologic changes. Some common, as well as some rare, diseases are believed to be of allergic origin, but the proof is either incomplete or disputed; rheumatic fever, periarteritis nodosa, rheumatoid arthritis, acute pancreatitis, lupus erythematosus disseminata, glomerulonephritis, scarlet fever and infectious mononucleosis are but a few examples. All have been inculpated because of clinical or historical similarities to serum sickness or accelerated allergic responses in both man and animals and because of the anatomic changes noted from time to time in material obtained at autopsies. These data to date have been totally inadequate for the construction of a well documented catalog of human immunopathology. This lack has blocked and continues to block a wider appreciation and acceptance of the anaphylactic interpretation of disease.

The universal use of sulfonamide compounds and the discovery that they can act as antigens capable of eliciting fatal reactions have, for the first time, made possible the study of a large number of relatively slow but fatal anaphylactic reactions. Because of these circumstances, the lesions discovered and the problems suggested by 5 cases of anaphylactic death following therapeutic use of sulfonamide compounds are presented.

REVIEW OF LITERATURE

The phenomenon of anaphylactic death has fascinated immunologists and some pathologists since Portier and Richet [1] recognized the significance of the fulminating fatal syndrome induced in some of their dogs. The anatomic changes accompanying this type of profound shock and subsequent death in both animals and man are so limited by the rapidity of the reaction that only the demonstration of a passive transfer of sensitivity (Prausnitz-Küstner reaction) in conjunction with an evaluation of the past history and the circumstances of death can establish the cause of the sudden death.

The production of local lesions by intrinsically harmless proteins (Arthus [2]) opened the door to the anatomic study of both local and generalized anaphylaxis. Since then the results of many investigations of the morphologic evidence of antigen-antibody reaction have been published, and numerous variations of Richet's and Arthus' fundamental experiments have led to the recognition of certain lesions as characteristic of (if not specific for) the hyperergic tissue response.

Von Pirquet [3] and Shick described in accurate detail a "unique" anaphylactic reaction in man which occurred eight to twelve days after a primary injection of horse serum. The syndrome was marked by a high temperature, cutaneous rashes (sometimes moribilliform or scarlatiniform), a tendency toward leukopenia, transient arthritis, lymphadenopathy, subcutaneous edema and albuminuria. This clinical process they named *Serumkrankheit* (serum sickness).

When, in 1917, Landsteiner [4] and Lampl demonstrated the mechanism whereby nonallergenic substances (simple chemical compounds) became allergens, the basis of a real understanding of drug allergy was laid.

Allergic reactions elicited by nonprotein drugs have been described so often and so regularly in medical journals that few well informed persons were skeptical when, in 1937, Hageman and Blake [5] reported the serum-sickness-like reactions of a group of patients who were treated with sulfanilamide. Goodman and Levy [6] were among the first to suggest that the rash appear-

From the Department of Pathology, Medical College of Virginia.

1. Portier and Richet, C.: Compt. rend. Soc. de biol. **54**:170, 1902.

2. Arthus, M. M.: Compt. rend. Soc. de biol. **55**: 817, 1903.

3. von Pirquet, C.: Jahrb. f. Kinderh. **62**:537, 1905.

4. Landsteiner, K.: The Specificity of Serological Reactions, Springfield, Ill., Charles C Thomas, Publisher, 1936.

5. Hageman, P. O., and Blake, F. G.: J. A. M. A. **109**:642, 1937.

6. Goodman, M. H., and Levy, C. S.: J. A. M. A. **109**:1009, 1937.

ing after treatment with sulfanilamide was the result of hypersensitivity, and while cutaneous tests in their 2 cases were respectively negative and doubtful, readministration of a small dose of the drug by mouth promptly resulted in a typical itching reaction of the skin. Schlesinger and Mitchell [7] studied the course of eruptions in children treated with sulfanilamide and noted a "natural history" of the rash marked by prodromal fever, transient leukopenia and a morbilliform and occasionally a scarlatiniform rash, often associated with splenomegaly, increased capillary fragility and in some cases arthritic symptoms.

Schönholzer [8] demonstrated that azosulfamide is bound to the serum albumin, and Davis,[9] succeeded in conjugating sulfonamide compounds to human blood serum by procedures following the methods pioneered by Landsteiner and Lampl. The results were confirmed by Wedum [10] and Gerber and Gross.[11] Wedum, using human and rabbit serum, as well as egg albumin, as the protein portion of the antigenic molecule, was able to produce anaphylactic shock, positive intradermal reactions, and, furthermore, with appropriately prepared antibodies, in vitro precipitation of the antigen. Gerber and Gross likewise demonstrated the antigenicity of conjugated sulfonamide compounds by producing anaphylaxis and the Shwartzman phenomenon in guinea pigs and rabbits.

Schlesinger and Mitchell,[7] using conjugated sulfanilamide, encountered the difficulties that had been met by past investigators in the field of drug allergy: They were unable to elicit in hypersensitive patients a positive reaction with scratch, patch or intradermal tests. Attempts to demonstrate hypersensitivity by means of the Prausnitz-Küstner reaction likewise failed. Because of these difficulties, doubt was expressed by many as to the validity of the anaphylactic concept of the reactions following treatment with sulfonamide compounds. More recently, however, Shaffer, Lentz and McGuire [12] have reported the production of a positive Prausnitz-Küstner reaction to sulfathiazole with serum from persons who had reacted to the drug a second time.

Leftwich [13] has done much to dispel any remaining skepticism by utilizing as test material the blood serum of patients receiving a sulfonamide drug in the course of therapy. Reasoning that the drug must be present in the blood stream as a protein conjugate, he inoculated intradermally 0.05 cc. of a serum known to contain conjugates into 30 persons who had reacted to sulfonamide compounds with a typical hypersensitive pattern. Twenty-eight of these persons promptly responded to the homologous sulfonamide conjugate by wheal formation at the site of inoculation; 2 did not react. As a control, 26 persons who had received treatment without reacting were tested in a similar manner; 24 showed no reaction, and only 2 reacted. The specificity of the cutaneous reactions was demonstrated by the fact that only 3 of the sensitive patients reacted to a nonhomologous conjugate. This form of cross sensitization was also encountered by Wedum [10] and by Gerber and Gross [11] in their experimental work, and has been observed in the course of human therapy.

Since morphologic changes which are considered characteristic of anaphylactic states have been noted in immunopathologic experiments, it was natural that similar lesions should be sought in persons who died during or after reactions of an allergic type following treatment with sulfonamide compounds. Numerous isolated instances and a few series of cases of death due to the effects of sulfonamide drugs have been reported in the literature; most of the authors have been concerned with the mechanism of urolithiasis medicamentosa or with the fatal blood dyscrasias agranulocytosis and hemolytic anemia. Since mechanical uremia lies outside the scope of this paper, it will not be further considered. The two blood dyscrasias are yet to be encountered in the autopsy room of the Medical College of Virginia, and only their minimal and theoretic expressions, leukopenia and erythrophagocytosis, will be discussed.

Cutts, Burgess and Chafee [14] encountered one death in a series of patients treated with sulfathiazole. On the eighth day of therapy a generalized rash appeared. Because of developing oliguria, the drug was discontinued on the eleventh day. However, the secretion of urine decreased to total anuria. In the autopsy protocol the kidneys were said to have shown tubular degeneration with foci of necrosis and interstitial round cell infiltration containing some neutrophilic poly-

7. Schlesinger, E. R., and Mitchell, W. L.: Am. J. Dis. Child. **56**:1256, 1938.

8. Schönholzer, G.: Klin Wchnschr. **19**:790, 1940.

9. Davis, D. B.: Science **95**:78, 1942.

10. Wedum, A. J.: J. Infect. dis. **70**:173, 1942.

11. Gerber, I. E., and Gross, M.: J. Immunol. **48**: 103, 1944.

12. Shaffer, B.; Lentz, J. W., and McGuire, J. A.: J. A. M. A. **123**:17, 1943.

13. Leftwich, W. B.: Bull. Johns Hopkins Hosp. **74**:26, 1944.

14. Cutts, M.; Burgess, A. M., and Chafee, F. H.: New England J. Med. **223**:762, 1940.

morphonuclear leukocytes. This was one of the earliest cases in which anuria was reported as not due to mechanical obstruction.

Erganian and Doval [15] had a similar experience with a child in whom anuria developed following readministration of sulfathiazole. The kidneys showed marked tubular degeneration, and although concretions were present in the pelves, the authors believed that the anuria was due in large part to the tubular damage.

Monto [16] described 3 cases of chemotherapeutic anuria encountered within a relatively short time at the Henry Ford Hospital. He was convinced that the failure of the kidneys was due to the nephrotic changes and not to crystalluria.

Since the lesions of the fatal reactions are generalized and not limited to the kidneys, the paper by Lederer and Rosenblatt,[17] soon followed by that of Merkel and Crawford,[18] gave the first detailed and balanced morphologic picture of such reactions. These authors were not primarily concerned with the problem of anaphylaxis, confining themselves to anatomic descriptions, although Lederer and Rosenblatt suggested that anaphylaxis might in part account for the nonbacterial foci of necrosis which stood in the foreground of the observed changes. These foci were surrounded by cellular exudates whose components, monocytes, lymphocytes and neutrophilic leukocytes, varied in proportion from case to case, with the monocytic elements predominating. They were described in the following organs: liver, spleen, lymph nodes, marrow, lungs, heart, kidneys, adrenal glands and pancreas. In addition, the convoluted tubules of the kidneys were so degenerated as to justify application of the term "nephrosis" in most cases. Interstitial myocarditis was observed by Lederer and Rosenblatt in 2 instances, accompanied in case 3 by a heavy monocytic mantling of some of the coronary arteries.

No characteristic pulmonary lesion was encountered; foci of consolidation and necrosis were seen.

The liver was the most frequent site of foci of necrosis; these were small and left the structure of the organ essentially intact. Kupffer cells were prominent, and in case 2 the portal fields were markedly infiltrated by monocytes and occasional neutrophilic leukocytes.

In every instance in which the spleen was histologically examined it contained areas of ischemic necrosis. Identical lesions of the lymph nodes were particularly well described by Merkel and Crawford.[18]

Rich [19] recognized the relationship between lesions like those of periarteritis nodosa which he observed in 6 patients who had received massive serum therapy and the serum sickness which preceded the death of 5. A seventh patient, receiving no serum but only sulfonamide drugs, showed the same lesions as the preceding 6. This observation was confirmed a short time later by investigation of a second instance of reaction to a sulfonamide compound.[20] The lesions seen by Rich were primarily vascular and consisted of fibrinoid necrosis of the walls of small arteries, which had rich adventitial collars of monocytes and occasional polymorphonuclear leukocytes. In addition, in 3 of the cases of serum sickness interstitial myocarditis and focal necrosis of the lymph nodes were noted. In the 2 cases of reaction to sulfonamide compounds aseptic, widely distributed foci of necrosis of the type described by Lederer and Rosenblatt [17] were seen; furthermore, in the second of these 2 cases the same type of interstitial myocarditis, interstitial nephritis and a unique form of pancreatitis were observed. The infiltrating cells in all organs were chiefly monocytes, lymphocytes and neutrophilic and occasionally eosinophilic polymorphonuclear leukocytes.

Many of these lesions had previously been described by numerous authors studying experimental anaphylaxis in animals.

The latest contribution in this field is the work of Rich and Gregory,[21] who induced what Fleischer and Jones [22] first described as the equivalent of serum sickness in rabbits. Postmortem study of these animals revealed all the characteristic changes of protein anaphylaxis,[23] the lesions being comparable in appearance and distribution to those observed by Rich in human serum sickness and reaction to sulfonamide drugs.

15. Erganian, J. A., and Doval, J. H.: J. Lab. & Clin. Med. **28**:808, 1943.

16. Monto, R. W.: Ohio State M. J. **38**:925, 1942.

17. Lederer, M., and Rosenblatt, P.: J. A. M. A. **119**:8, 1942.

18. Merkel, C., and Crawford, R. C.: J. A. M. A. **119**:770, 1942.

19. Rich, A. R.: Bull. Johns Hopkins Hosp. **71**: 123, 1942.

20. Rich, A. R.: Bull. Johns Hopkins Hosp. **71**: 375, 1942.

21. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **72**:65, 1943.

22. Fleischer, M. S., and Jones, L.: J. Exper. Med. **54**:597, 1931.

23. (*a*) Heinlein, H.: Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **20**:274, 1937. (*b*) Klinge, F.: Beitr. z. path. Anat. u. z. allg. Path. **83**: 185, 1929. (*c*) Vaubel, E.: ibid. **89**:374, 1932. (*d*) Apitz, K.: Virchows Arch. f. path. Anat. **289**:46, 1933.

Gessler [24] has recently contributed a description of 3 cases of death caused by reaction to sulfonamide compounds, in which the pathologic changes were similar to those just described.

No attempt has been made to review extensively the immense literature of anaphylaxis and reactions to sulfonamide compounds. However, a number of excellent reviews are available and are listed among the references.[25]

REPORT OF CASES

CASE 1.—A 23 year old Negro woman was given sulfathiazole by her physician because of abdominal pain. She rapidly grew worse, and after four days was referred to St. Philip's Hospital. In the emergency room her appearance of extreme shock was confirmed by a blood pressure reading of 70 systolic and 50 diastolic. Her temperature was recorded as 105 F., and the pulse rate as 110 per minute. A blood count revealed 4,800,000 erythrocytes and 12,650 leukocytes per cubic millimeter. The urine showed albumin (3 plus) and rare hyaline casts. Chemical studies of the blood were reported as showing nonprotein nitrogen 190 mg., sugar 143 mg. and sulfathiazole 1.8 mg. per hundred cubic centimeters. The patient died the day after admission to the hospital. The clinical diagnosis was uremia due to sulfathiazole.

Gross Examination.—The spleen weighed 190 Gm. Its capsule was covered by a thin layer of fibrin and was marked by small, prominent, firm, confluent brown-red areas, which on section showed pyramidal configuration with the bases on the capsule. The surrounding tissue was not remarkable in appearance.

The left fallopian tube was bound to its ovary by fibrous adhesions; the fimbriae were accreted and sealed the lumen.

The right and left kidneys weighed respectively 220 and 200 Gm.; the fibrous capsules stripped with ease, revealing smooth lobulated surfaces. Sections showed pale bulging surfaces with well demarcated corticomedullary boundaries. The pelves were not remarkable.

Microscopic Examination.—The myocytes of the heart were fragmented, and the intervening spaces were widened by edema. A sparse interstitial monocytic infiltration was present, particularly prominent about the small vessels.

Sections of liver were characterized by early fragmentation of the cords. The portal fields were infiltrated by monocytes, eosinophilic leukocytes and occasional plasma cells. Stille's spaces were wide; the sinusoids were moderately congested and contained occasional macrophages, which were filled with leukocytes (fig. 1) and erythrocytes. The parenchymal cytoplasm was the seat of cloudy swelling. Kupffer's cells were prominent.

The follicles of the spleen were enlarged and showed marked central hyperplasia and necrosis. The reticuloendothelium was hyperplastic and displayed active erythrophagocytosis and leukophagocytosis. The firm pyramidal zones already described grossly were areas of ischemic necrosis. Necrobiotic neutrophilic leukocytes and much basophilic debris marked the areas of necrosis, which were demarcated by a zone of reaction.

Lymph nodes from various sites showed diffuse hyperplasia; some contained macrophages similar in all respects to those described in the spleen. Numerous eosinophilic and neutrophilic polymorphonuclear leukocytes were scattered about the pulp.

The renal interstices were infiltrated by monocytes, plasma cells and occasional eosinophilic leukocytes. These showed a tendency toward focalization about glomeruli and small vessels. The glomerular tufts contained little blood, and in a few instances the number of endothelial cells appeared to be increased. The glomerular spaces contained precipitated protein, and the parietal lining was composed of cuboidal cells. The tubules showed cloudy swelling of their epithelium but no necrosis. Examination of the peripelvic fat clearly showed the ubiquitous exudate described in the heart, the liver and the kidneys.

Pathologic Diagnosis.—Interstitial myocarditis; serous hepatitis; interstitial nephritis; focal splenic necrosis (Feitis); generalized lymphadenitis; salpingitis on the left side; erosions of the cervix; cavernous hemangioma of liver.

CASE 2.—A white man 54 years old was referred from a tuberculosis sanatorium to the Medical College of Virginia Hospital for treatment of "vague urinary disturbances" and abdominal discomfort of three months' duration. On admission the temperature, the pulse and respiratory rates and the blood pressure were well within normal limits. The urine revealed no albumin and no sugar; the blood count was not remarkable, and the blood nonprotein nitrogen was reported as 36 mg. per hundred cubic centimeters. A phenolsulfonphthalein test for renal function resulted in the excretion of 53 per cent of the injected total in two hours and twenty-five minutes. The unusual interval of time for this procedure was entailed by the patient's difficulty in micturition, due to an enlarged prostate gland.

Physical examination did not produce any clinical evidence of disease other than prostatic hypertrophy.

For some unrecorded reason, 240 grains (15.5 Gm.) of sulfathiazole was prescribed and administered from the day of his admission—May 19 to May 23, 1943.

Roentgenologic investigation of the kidneys on May 22 revealed an enlarged minor upper calix in the left organ. Urine from the corresponding ureter contained 3 to 4 erythrocytes per high power field. The contralateral kidney excreted normal urine. After the first few days of sulfathiazole medication the patient frequently vomited, refused food and was given large amounts of fluid intravenously. On May 29 he complained that he had not voided for five or six days. Blood taken for chemical studies on May 28 contained 112 mg. of nonprotein nitrogen and 8.0 mg. of creatinine per hundred cubic centimeters.

The temperature, which had been normal up to May 29, began to rise and remained at a level of about 102 F. for the remainder of his stay.

On May 30 and 31 he was given 30 grains (2 Gm.) of sulfathiazole intravenously in a desperate attempt to stave off death, which occurred thirteen days after his admission.

Gross Examination.—The left lung weighed about 750 Gm. Fibrinous bands bound the parietal and the visceral pleura in the axillary line. The organ was subcrepitant throughout except for some marginal emphysema. Section brought to view foci of consolidation in both lobes. The right lung weighed 500 Gm. and was essentially similar to the contralateral organ. The bronchial lymph nodes draining the right lung were enlarged and contained calcific concretions and soft caseous gray-white material.

24. Gessler, C. N.: South. M. J. **37**:365, 1944.

25. Ratner, B.: Allergy, Anaphylaxis and Immunotherapy, Baltimore, Williams & Wilkins Company, 1943. Longcope, W. T.: Medicine **22**:251, 1943. Simon, M. A.: Am. J. M. Sc. **205**:439, 1943. Heinlein.[23a]

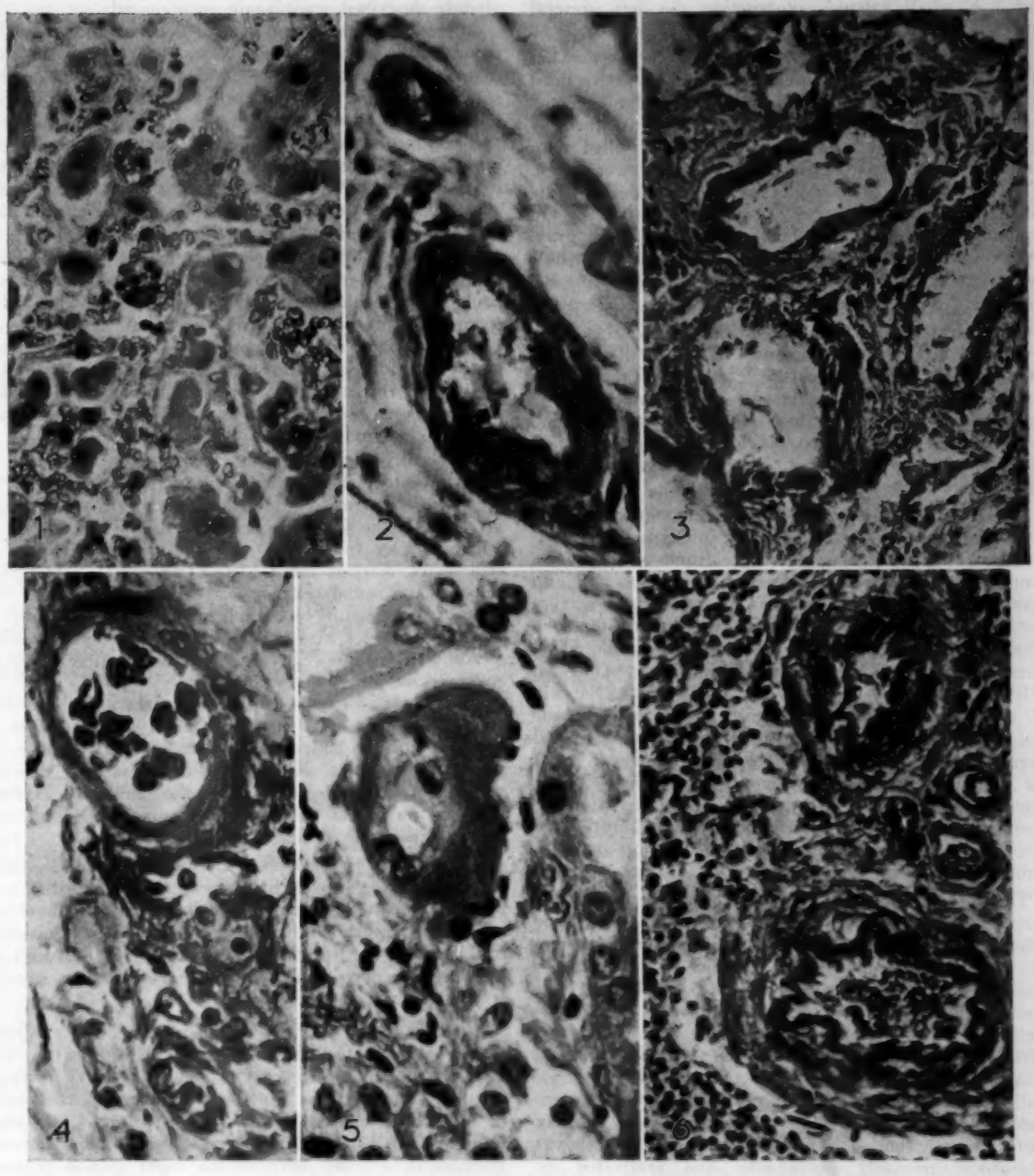

Fig. 1 (case 1).—Serous hepatitis: Trabeculae are moderately fragmented, Disse's spaces are prominent, and within a sinusoid is a macrophage filled with leukocytes (× 441.6).

Fig. 2 (case 2).—Fibrinoid necrosis of a small coronary artery (× 441.6).

Fig. 3 (case 2).—Interstitial pneumonia: The infiltrating leukocytes lie within edematous septums; the alveoli are outlined by fibrin membranes (× 165.6).

Fig. 4. (case 2).—Necrotizing arteritis in renal pelvis and fibrinoid degeneration of the adjacent connective tissue (×653).

Fig. 5 (case 2).—Necrosis of an isolated renal convoluted tubule surrounded by leukocytes. The epithelium of neighboring tubules shows marked degeneration (× 653).

Fig. 6 (case 2).—Intimal fibrinoid degeneration of splenic arteries and arterioles (× 331).

The prostate gland was moderately enlarged, and its median lobe impinged on the trigonum vesicae. The bladder contained no urine, and its mucosa was edematous. A small calculus obstructing the left ureteral orifice was removed, revealing uninjured mucosa.

The left ureter and the renal pelvis were somewhat dilated but, except for one calix, were everywhere lined by normal-appearing gray mucosa. The calix excepted measured about 2 cm. in diameter and was lined by black-stained tissue. Its lumen was partly filled with similar-colored viscid material; no calculi were seen. The capsules of both kidneys stripped with moderate difficulty, revealing coarsely granulated surfaces. On section, the tissue planes bulged and were livid gray. Structural details were obscured, and the corticomedullary boundary was poorly defined.

Microscopic Examination. — The myocardial fibers were separated by marked interstitial edema; they were fragmented but not necrotic. The small arteries were marked by homogeneous swelling of the intima and vacuolation of the media (fig. 2). The nuclei of the myocytes in some vessels were distorted, some showing pyknosis and others karyorrhexis. A minimal exudate of monocytes was present in the interstices, chiefly about the vessels.

Study of numerous sites in all pulmonary lobes revealed edematous alveolar septums, infiltrated by mononuclear cells, many of which were frank macrophages, containing vacuoles and occasionally a leukocyte, an erythrocyte or both. Numerous interalveolar arterioles and capillaries were filled with conglutinated thrombi. The alveolar walls were outlined by acidophilic fibrin membranes, which characterized the lesion (fig. 3). Within the air sacs was an exudate consisting largely of macrophages, monocytes, fibrin and neutrophilic leukocytes. The proportions of these elements varied from one region to another. Nowhere, however, were the polymorphonuclear leukocytes numerous. Large macrophages, in some loci assuming the proportions of giant cells, filled entire alveolar groups. Many of the pulmonary arteries showed medial vacuolation and subintimal leukocytic exudate.

The renal structure was intact. The abscess of the calix in the left kidney was lined by granulation tissue infiltrated by macrophages, its lumen containing numerous neutrophilic leukocytes and monocytes; the process was sharply delimited from the renal parenchyma. Sections of other calices revealed completely intact epithelium of the transitional type. The submucosa was diffusely infiltrated by monocytes, lymphocytes and occasional eosinophilic leukocytes. Small arteries, whose walls showed the changes described in the heart, were likewise present. Some of the vessels were frankly necrotic, and the surrounding connective tissue was edematous, intensely eosinophilic and infiltrated by monocytes (fig. 4). This form of fibrinoid connective tissue necrosis was focal in distribution. Both organs contained numerous small fibrous cortical scars, which were subcapsular, and contained completely fibrotic glomeruli. The tubules within these foci were atrophic, and the interstices were infiltrated by lymphocytes. A second exudate of different composition—monocytes, plasma cells, eosinophilic leukocytes and occasional neutrophilic leukocytes—was diffusely spread throughout the interstices of both the cortex and the medulla. The glomeruli on the whole were relatively avascular. No increase in endothelial or epithelial cells of the capillary loops was apparent; however, the cells of the parietal leaf of Bowman's capsule were hypertrophied, some having assumed almost cuboidal appearance. Isolated convoluted tubules were necrotic (fig. 5); the greatest number showed only marked cloudy swelling. No evidence of tuberculosis was seen in either kidney. Arterial medial edema and nuclear changes of the type already described were again encountered.

A section of the aorta showed marked fibrous thickening of the intima, which contained foci of atheromatosis; adherent was a laminated thrombus. The subjacent intima was infiltrated by neutrophilic polymorphonuclear leukocytes; at the junction of the intima and the media was an exudate of monocytes and polymorphonuclear leukocytes invading the innermost zone of the media. Within this region the myocytes were edematous and the nuclei distorted. The adventitia was the seat of a similar but moderate cellular exudate.

The sinusoids of the spleen were markedly congested; the follicles were enlarged and contained numerous neutrophilic leukocytes. The reticuloendothelial cells were hyperplastic, and some germinal centers were necrotic. Fibrinoid homogenization of the intimal coat of the arterioles was seen in almost all follicles (fig. 6). Infiltrating beneath the endothelium of some of the larger vessels were numerous monocytes, lymphocytes and rare polymorphonuclear leukocytes.

The centrolobular sinusoids of the liver were dilated and congested. The parenchymal cells bordering these areas were compressed, and their cytoplasm was granular. Kupffer cells were hypertrophied and Disse's spaces widened. Occasional foci of a few polymorphonuclear leukocytes marked these loci. The portal fields contained some round cells, and with the exception of the arteries the structures were not remarkable. The arteries and the arterioles were edematous, and the muscle nuclei showed the changes already described in the vascular myocytes of the other organs.

The lymph node removed from the right main bronchus was a caseous mass of necrotic tissue surrounded by a zone of fibrosis and characterized by the presence of giant cell tubercles. Nodes from the mesentery showed reticuloendothelial hyperplasia of the same type as that noted in the spleen, and a minimal amount of erythrophagocytosis.

Pathologic Diagnosis. — Generalized arteritis; acute thromboaortitis; interstitial pneumonia; interstitial nephritis; generalized acute lymphadenitis; tuberculous bronchial lymphadenitis; chronic suppurating abscess of a calix of the left kidney; calculus of the left ureter, mild hydronephrosis of the left kidney, benign hypertrophy of the prostate gland.

CASE 3.—A 64 year old white woman was admitted to the Medical College of Virginia Hospital Jan. 24, 1944 because of a psychosis. During the previous year she had suffered from a persistent cutaneous rash said to have been caused by sensitivity to soap; she was treated for this by numerous physicians, without success. Because of a small burn of the right gluteal region, sulfanilamide dressings were applied January 29. Up to this date the patient was organically well except for hypertension (170 systolic and 110 diastolic). On January 30 the oral temperature was found to have risen to 101.3 F., and sulfadiazine therapy was consequently instituted, a total of 350 grains (22.5 Gm.) being administered during the following four days. By February 1 the oral temperature had risen to 104 F. and remained at about that level until February 6, when the drug was discontinued. On February 4 a generalized maculopapular rash spread over the patient's body. The clinical interpretation of her condition at this time was pneumonia. Since the sulfadiazine therapy appeared to have little beneficial effect, it was discontinued; however, the sulfanilamide dressings were not but were applied until the patient's death, February 8.

On her admission to the hospital, her urine had shown no abnormalities. On the day of her death it contained albumin (2 plus), 4 to 6 leukocytes per high power field and many granular casts. Unfortunately, no studies of renal function were undertaken except for a determination of the nonprotein nitrogen of the blood on admission: 29 mg. per hundred cubic centimeters. The sulfadiazine levels on February 3 and 5 were, respectively, 17.6 and 18.6 mg. per hundred cubic centimeters. A hematologic study on February 3 revealed 3,800,000 erythrocytes and 12,500 leukocytes per cubic millimeter. The differential count was 91 per cent neutrophilic polymorphonuclear leukocytes, 5 per cent lymphocytes and 4 per cent eosinophilic leukocytes.

Gross Examination.—A maculopetechial rash covered the entire body. The efflorescence was confluent on the backs of the hands, the elbows and the thighs. A recent second degree burn, 8 cm. in the longest dimension, was present in the right gluteal region.

The left pleural cavity contained 600 cc. and the right 500 cc. of clear straw-colored fluid.

The right and the left lung weighed, respectively, 725 and 500 Gm. The pleural cavity of the right hemithorax was largely obliterated by fibrous adhesions. The lung was firm and subcrepitant throughout. On section the blood could be expressed with ease; no areas of consolidation were visible. The left lung was crepitant throughout except for several small areas in the lower lobe.

Each kidney weighed 150 Gm. The capsules stripped with difficulty, revealing scarred surfaces. On bisection of the organs, the cortices appeared narrowed, but the structures were essentially not remarkable.

Microscopic Examination.—The myocardial interstices were occupied by a cellular exudate composed of monocytes, some neutrophilic and eosinophilic polymorphonuclear leukocytes and histiocytic cells possessing a large amount of cytoplasm, some showing active erythrophagocytosis. The exudate was particularly rich about vessels. The myocytes were fragmented.

Numerous sections from both lungs revealed foci of consolidation about bronchioles. The alveoli contained an exudate composed of neutrophilic leukocytes, monocytes and basophilic nondescript debris and fibrin. In these areas the bronchiolar epithelium was desquamated. Two sections showed marked alveolar capillary congestion. Within the septums were numerous leukocytes similar in type and distribution to those described in the heart. Many of the alveoli were lined with fibrinous membranes. Conglutinated thrombi filled some of the interalveolar capillaries.

In the kidneys there were foci of cortical fibrosis wherein the glomeruli were completely fibrosed and hyalinized. A dense round cell exudate was present in these areas. Aside from these changes the glomeruli were not remarkable; however, the epithelium of the convoluted tubules showed cloudy swelling, far advanced in some foci. In these areas small collections of monocytes were present. The arteries showed intimal fibrosis and thickening.

Focal cellular exudates consisting of monocytes and neutrophilic leukocytes obscured the acinous structure of the pancreas. The interstices were edematous, and the vessels were surrounded by cellular mantles similar in composition to those seen in the parenchymal lobules. The media of small arteries was thickened and the myocytic structure obscured by fibrinoid necrosis. The nuclei of the muscle cells were distorted and pyknotic, and many of the arterioles were filled with conglutinated thrombi.

The hepatic portal fields were prominent because of a heavy monocytic exudate, among which were neutrophilic and eosinophilic leukocytes as well as plasmatoid cells. In some areas the connective tissue matrix stained the uniform deep red of fibrinoid necrosis. Occasional small hepatic arteries showed changes similar to those seen in the pancreas (fig. 7). Kupffer cells were easily visualized because of wide Disse's spaces. The hepatic cords were intact, but cloudy swelling and fat vacuoles were seen throughout the organ.

The splenic follicles were hyperplastic; an eosinophilic homogeneous substance was present in many germinal centers. The pulp was congested, and numerous eosinophilic and neutrophilic leukocytes were present.

Pathologic Diagnosis.—Generalized arteritis; interstitial myocarditis; serous hepatitis; acute interstitial pancreatitis; interstitial and focal pneumonia; bilateral hydrothorax; fibrous pleural adhesions; generalized atherosclerosis.

CASE 4.—On June 6, 1944 a 53 year old white woman suddenly and without prodrome began to suffer from headache, chills and fever. She was treated by her local physician with tablets not believed to contain any sulfonamide compound. Because her condition grew steadily worse, a second physician was consulted. He administered 30 grains (1.92 Gm.) of sulfathiazole in two doses and then, suspecting the possibility of Rocky Mountain spotted fever because of the appearance of an erythematous macular rash, sent her to the Medical College of Virginia Hospital. On admission the patient's temperature was 105 F. The urine revealed albumin (1 plus) and 10 to 18 leukocytes and 100 erythrocytes per high power field. A blood count showed 4,200,000 erythrocytes and 18,200 leukocytes per cubic millimeter. Although it was believed that Rocky Mountain spotted fever was the most plausible diagnosis, blood taken for agglutination tests on January 15 (nine days after the onset of the disease) was reported as showing no agglutinins for Proteus X-19 or X-2 or for organisms of the Eberthella and Salmonella groups. On admission the patient had been given 15 grains (0.96 Gm.) of sulfacetimide (paraaminobenzene sulfonylacetylimide) by mouth and 60 grains (3.84 Gm.) of sulfadiazine intravenously; a further dose of 15 grains (0.96 Gm.) of sulfathiazole was administered by mouth June 12, 1944. Because it was believed that sulfonamide compounds were ineffective against rickettsial diseases, their use was discontinued. The patient showed no response to therapy, and on June 14 a second blood count showed relative leukopenia (5,800 leukocytes per cubic millimeter). On June 16 generalized edema was observed; the patient died in uremia on June 18.

Gross Examination.—The petechial rash was present in the greatest concentration on the skin of the upper part of the abdomen and the backs of the hands and was scattered over the remainder of the body. The hands and feet showed pitting edema. In the axillary and inguinal regions the lymph nodes could be readily palpated. Each pleural cavity contained about 100 cc. of clear yellow fluid.

The spleen was bound to the diaphragm and the lateral posterior abdominal wall by fine fibrous bands. The organ's consistency was moderately reduced, and on section the surface was gray-red. The parenchyma on section bulged and could be scraped away with ease.

The kidneys weighed, left, 275 Gm., right, 150 Gm. When the adipose and fibrous capsules were stripped, pale surfaces were revealed, and a few small cysts filled with clear fluid were visible on the surfaces of both organs.

The consistency of the liver was reduced, and on incision the cut surfaces were yellow-brown and greasy. The central venules were prominent, and the usual lobular markings were obscured.

The axillary, inguinal, para-aortic and mesenteric lymph nodes were enlarged, and when sectioned they revealed homogeneous pale brown surfaces.

Microscopic Examination.—The myocardial fibers were fragmented, and the interstices were characterized by an exudate of histiocytic monocytes, plasma cells and very occasional neutrophilic polymorphonuclear leukocytes (fig. 8). The exudate was most prominent in the inner third of the myocardium and the zone adjacent to the epicardium.

The hepatic structure was disorganized by marked fragmentation of the trabeculae and early necrosis of the cells about the central venules. The portal spaces were infiltrated by numerous monocytes and a few neutrophilic polymorphonuclear leukocytes. Eosinophilic homogenization of the walls of small arteries was visible in some of the portal fields. The nuclei of the myocytes of these vessels showed distortion and karyorrhexis. The hepatic veins contained many liver cells showing all stages of degeneration.

The interstices of the pancreas were edematous and sparsely infiltrated by monocytes. The islets of Langerhans were not remarkable.

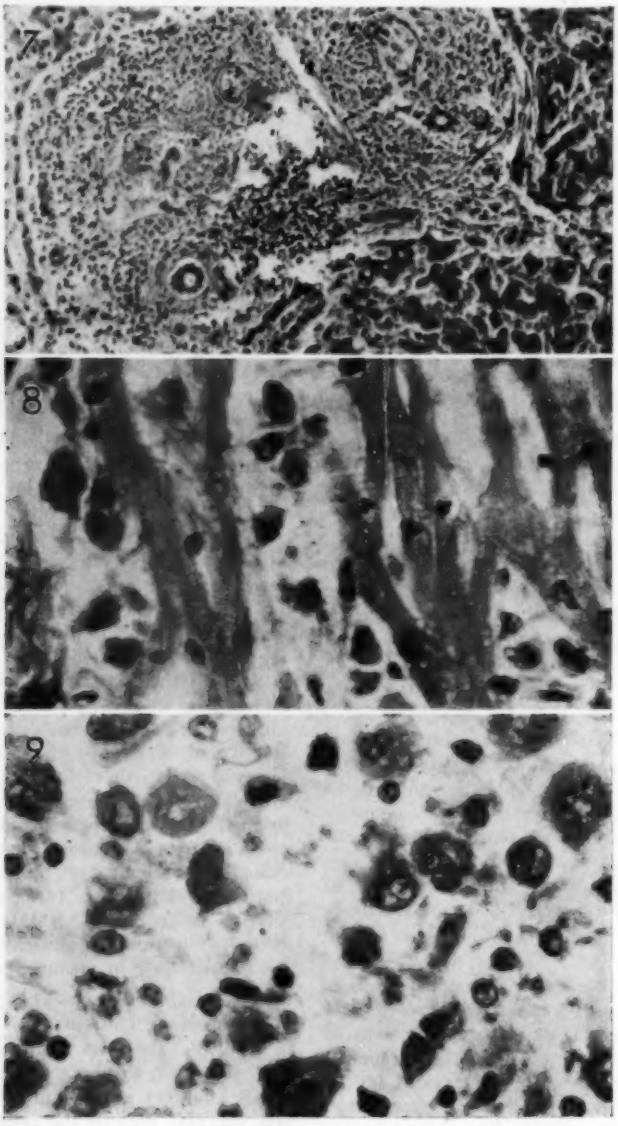

Fig. 7 (case 3).—Portal field of the liver infiltrated by round cells; fibrinoid necrosis of a small hepatic artery (× 135).

Fig. 8 (case 4).—Characteristic histiocytic interstitial myocarditis (× 540).

Fig. 9 (case 4).—Sinusoid of a lymph node filled with proliferated reticuloendothelial cells; many are frank macrophages containing erythrocytes (× 765).

Both kidneys presented typical interstitial infiltrates of monocytes, neutrophilic polymorphonuclear leukocytes, lymphocytes and plasma cells. These exudates were thickest about glomeruli and small vessels. The glomerular loops contained little blood, many tufts were bloodless, and precipitated protein substance lay within

Bowman's spaces. The convoluted tubules were bright pink and showed marked cloudy swelling; in some instances the nuclei were undergoing karyorrhexis. Many of the tubules contained hemoglobin casts, within which erythrocytes were still recognizable. No crystals were seen. The perirenal and peripelvic connective and adipose tissues were infiltrated by inflammatory cells of the same type as those described in the parenchyma. An occasional segment of the wall of a small artery was converted into homogeneous fibrinoid material.

Large zones of ischemic necrosis were observed in the spleen. Within these areas the sinusoids contained only erythrocytic shadows; connective tissue trabeculae were indistinct, and all nuclei were pyknotic or broken up into small particles, giving a blue cast to the necrotic zones. In the viable regions lymphoid follicles were hyperplastic and showed various stages of central necrosis. The intima of the pencil arteries was thickened and eosinophilic, and medial nuclei were undergoing early karyorrhexis. The subendothelium was infiltrated by monocytes, including occasional polymorphonuclear leukocytes. The reticuloendothelial cells were prominent. The sinusoids of both the medulla and the coretx were filled with large mononuclear cells, many showing phagocytosis of erythrocytes and leukocytes. Nowhere, either leading to or in the regions of necrosis, could obstruction of vessels be demonstrated.

Histologic study of lymph nodes taken from various sites showed a more or less uniform appearance. There was marked reticuloendothelial hyperplasia, resulting in a filling of all the sinusoids with cells similar in all respects to those described in the spleen. The origin of these cells is demonstrated by their ability to phagocytose erythrocytes, lymphocytes and a small amount of hemosiderin (fig. 9). Lymphoid follicles were discernible only by their hyperplastic germinal centers. The capsules and the surrounding connective tissue were infiltrated by monocytes, plasmatoid cells and occasional polymorphonuclear leukocytes both neutrophilic and eosinophilic.

Sections of sternum, rib and vertebral marrow revealed large reticuloendothelial cells of the same type as those seen in both the spleen and the lymph nodes. They showed much phagocytosis of erythrocytes and leukocytes. No necrosis was seen.

The uterine myometrium was not remarkable; the endometrial glands were arranged in a typical proliferative pattern. The small uterine arteries showed homogeneous eosinophilic thickening of their intima.

The stratified squamous epithelium of the esophagus was represented by small islands showing essentially the normal structure. Between these areas of intact epithelium the surface was denuded of its lining. The submucosa was massively infiltrated by neutrophilic polymorphonuclear leukocytes, monocytes and occasional plasmatoid cells. The small arteries throughout the organ were characterized by vacuolation of the muscularis and distortion of the nuclei, many of which showed early karyorrhexis. Some were the site of typical foci of fibrinoid necrosis surrounded by monocytes, plasma cells and eosinophilic leukocytes. The smooth musculature of the organ showed fragmentation and nuclear pyknosis. The mediastinal connective tissue was edematous and infiltrated by inflammatory cells of the same type as those described about the vessels.

A small area of mucosa in the ileum was absent, and the base of the shallow ulcer was hemorrhagic. The small arteries showed typical fibrinoid necrosis, and again the characteristic monocytic exudate with its erythrophagocytic histiocytes was prominent; some of the vessels were filled with conglutinated thrombi.

Numerous sections of skin taken at various sites through the maculas contained small arteries in which the media was vacuolated. Some of the nuclei were absent; others were distorted and showed marked tinctorial abnormalities interpreted as early degeneration. Some of the vessel walls were homogeneous, characteristic of fibrinoid necrosis, and surrounded by the thin mantle of monocytes so frequently noted in other organs. The walls of the necrotic vessels were likewise infiltrated by the leukocytes. Many of these arteries were surrounded by extravasated erythrocytes. The entire subcutaneous fat was diffusely infiltrated by cells of the same type, some of which showed phagocytic activity. The dermis subjacent to the epithelium was edematous and similarly infiltrated.

Pathologic Diagnosis.—Generalized arteritis; interstitial myocarditis; interstitial nephritis; serous hepatitis; focal splenic necrosis (Feitis); ulcerating esophagitis and ileitis; generalized acute lymphadenitis.

CASE 5.—In this case, Dr. William Branch Porter as consultant recognized the syndrome, and Dr. James W. Eliot submitted the material to the department of pathology of the Medical College of Virginia.

A 51 year old white woman was treated, May 1, 1943, for acute pharyngitis with 45 grains (2.88 Gm.) of sulfadiazine daily. May 3, 1943, she was admitted to a hospital, where the therapy was continued. May 4, 22.5 grains (1.44 Gm.) of sulfanilamide was given, followed on May 5 and 6 by 37.5 grains (2.4 Gm.) of the same drug. About May 7 she "broke out over her chest, abdomen, back, and hips with urticarial wheals, one-half to one and one-half inches in diameter, white in the center and red at the periphery." The administration of sulfanilamide was thereupon suspended, but that of sulfadiazine was continued. The rash disappeared within "two or three days," and on May 13 treatment with sulfadiazine was also discontinued. She received no sulfonamide drug for the next eight days; then (May 21) 90 grains of sulfanilamide (5.76 Gm.) and 20 cc. of azosulfamide were given, the latter by intramuscular injection. About 25 cc. of azosulfamide was regularly administered until May 31, when all medication with sulfonamide drugs was again suspended. May 28, 135 grains (8.64 Gm.) of sulfanilamide was given, followed by a similar dose the next day. A disseminated rash appeared on the succeeding day (May 30) accompanied by congestion of the conjunctivas and a mildly icteric appearance of the scleras. Because renal function showed progressive impairment, with the blood urea nitrogen rising to 43 mg. per hundred cubic centimeters, a medical consultation was sought. The patient was seen by the consultant about June 1; at that time she was still covered by a maculopapular rash. Although the administration of sulfonamide compounds was immediately stopped and measures taken to stimulate renal function, the patient died June 4 in uremia.

The heart and blocks of lung, liver, spleen and gallbladder were received in formaldehyde.

Microscopic Examination.—The myocardial fibers were separated by edema; within the interstitial spaces was a diffuse exudate of histiocytes and plasmatoid cells, whose cytoplasm was markedly eosinophilic. Among these cells were some lymphocytes and occasional polymorphonuclear leukocytes. Phagocytosis of leukocytes was seen in some foci.

The parenchymal cords of the hepatic lobules were fragmented. In the central zones, the nuclei showed

early karyorrhexis, and the cell cytoplasm contained numerous vacuoles. Sinusoids were dilated, and Kupffer cells were prominent and vacuolated. Disse's spaces were distended, and a moderate number of polymorphonuclear leukocytes were scattered throughout the sinusoids and the portal fields.

Renal convoluted tubules showed degenerative changes running the gamut from marked cloudy swelling to necrosis, the latter being sharply focal; within these areas the cellular outlines and nuclei could no longer be seen. The lumens were filled with acidophilic material probably derived from desquamated necrotic epithelium. Hyaline casts were numerous and appeared in all segments of the nephrons. The glomerular capillaries contained few erythrocytes, and their basement membranes were thickened.

The peribronchial alveoli were filled with an exudate rich in monocytes, polymorphonuclear leukocytes and fibrin. The adjacent bronchioli contained purulent exudate, and their walls were infiltrated by both polymorphonuclear leukocytes and mononuclear cells.

Splenic follicles were not prominent; the sinusoids were packed with erythrocytes, and the endothelial cells were hyperplastic.

The small arteries in all organs examined were characterized by edema of the media and swelling of the intima. Some of the muscle nuclei showed tinctorial changes indicative of nuclear damage.

Pathologic Diagnosis.—Interstitial myocarditis; necrosis of renal tubules (nephrosis); serous hepatitis; focal pneumonia.

COMMENT

In general the tissues in the 5 cases were characterized by two related lesions: arterial changes (except in case 1) and generalized cellular exudate.

The arterial lesions differed in appearance; yet all were reflections of a linear progression from simple edema (which Rich [19] aptly compared to the edema of a cutaneous wheal) to frank necrosis. The nuclei of the myocytes underwent pyknosis or karyorrhexis, and a circumferential segment of the arterial wall lost its cellular detail and assumed the eosinophilia of fibrinoid necrosis (fig. 4). The earliest cellular components of the exudate, neutrophilic leukocytes and lymphocytes, appeared in the intima. Thereafter a moderate periadventitial exudate of lymphocytes, monocytes (some actively phagocytic), plasma cells and occasional eosinophilic and neutrophilic leukocytes made its appearance. The surrounding connective tissue matrix of some vessels underwent fibrinoid necrosis similar to that of the arteries themselves (fig. 4). Although none of the examples of necrotizing vascularitis seen was quantitatively comparable to the typical lesion of periarteritis nodosa, the basic pattern was so similar that it suggested a difference of intensity and duration of action rather than of quality of irritant.

The cellular exudate invading the connective tissue of the skin, the renal pelvis, the mediastinum, the gastrointestinal tract and other organs was similar in all respects to that mantling the smaller arteries. The most prominent component was a macrophage possessing a large amount of cytoplasm and displaying active phagocytosis not only of debris, where this was available, but of whole leukocytes and erythrocytes as well. Its nucleus was eccentrically situated, and it sometimes resembled (in the hemotoxylin and eosin preparation) a plasma cell so closely that only the presence of transitional types and the phenomenon of phagocytosis made differentiation possible.

The basic lesions of experimental protein anaphylaxis have been thoroughly investigated [26] and the overwhelming consensus is that the phenomenon is characterized by fibrinoid necrosis of both small arteries and connective tissue and the presence of a cellular exudate composed chiefly of monocytes, lymphocytes, plasma cells and eosinophilic and neutrophilic leukocytes. A decided tendency for the cells to arrange themselves perivascularly has likewise been recorded, and the suggestion has been repeatedly made that periarteritis nodosa in man may represent an anaphylactic phenomenon.[23a] Rich's [21] conclusions in this respect are the latest reaffirmation of this belief.

That the arterial lesions and the composition of the cellular exudate observed in the reactions following administration of sulfonamide compounds are similar in all respects to those of experimental anaphylaxis is apparent.

French and Weller,[27] examining the hearts of patients treated with sulfonamide drugs, noted an interstitial exudate containing large mononuclear cells of the "clasmatocytic type." All hearts of the present series showed interstitial myocarditis of this type. The cells of the exudate were similar to those observed by these two authors. The most prominent were macrophages of the same type as those described in the connective tissues. Phagocytosis of erythrocytes and leukocytes in the heart as seen in some of the cases of this series is rarely observed, and, although the term "clasmatocyte" is generally applied to cells capable of phagocytosis, French and Weller do not record its observation.

Interstitial myocarditis is the lesion most consistently noted in experimental anaphy-

26. Arthus.[2] Rich and Gregory.[21] Heinlein.[23a] Klinge.[23b] Vaubel.[23c] Apitz.[23d]

27. French, A. J., and Weller, C. V.: Am. J. Path. **18**:109, 1942.

laxis.[28] Clark and Kaplan[29] and Rich[19] saw this change in their cases of human serum sickness, and it has been repeatedly described in instances of fatal reactions to sulfonamide compounds.

The presence of the lesion in all 5 cases of this series is confirmation, in man, of the experimental observation that interstitial myocarditis is one of the commoner, perhaps the most frequent, of the expressions of generalized anaphylaxis.

In 4 of the cases the characteristic vascular lesions were readily seen in the heart (fig. 2). While the myocardial fibers showed marked degeneration in the areas of greatest cellular exudation, foci of necrosis such as those described by Lederer and Rosenblatt were not encountered.

Multiple ischemic infarction of the spleen was first described by Feitis in 1921. Since then approximately 29 cases have been reported,[30] in most of which the infarcts were caused by thrombosis of splenic arteries. However, several cases without vascular obstruction have been recorded. It is believed that cases 1 and 4 belong in the latter category. The infarcts involved not merely the follicles but the red pulp as well, and nowhere was occlusion of vessels demonstrable, although the small arteries in case 4 showed marked fibrinoid necrosis.

Explanations of this phenomenon are not easily formulated. Enzer[31] drew a parallel between Mallory's theory of hepatic sinusoidal obstruction by macrophages (by means of which Mallory explained the typical typhoid lesions of the liver) and the presence of numerous macrophages within the perifollicular sinusoids of the spleen in his case. Magnus,[32] who described a case of multiple splenic infarction without visible vascular occlusions, expressed the belief that some toxic factor may have injured the tissue, producing the necrosis.

It appears significant that in 2 of 5 cases in this small series the spleen showed a lesion which is so uncommon that up to 1938 only 29 instances had been recorded in the literature.

Numerous authors[33] have reported focal follicular necrosis of the spleen and the lymph nodes and a similar lesion of marrow in reactions to sulfonamide drugs. Necrosis of lymph nodes was observed in 2 of the cases of serum sickness studied by Rich[19] (cases 17250 and 12291). In the present series such lesions of the lymph nodes were not seen.

Phagocytosis was most prominent in these same areas (fig. 9). The reticuloendothelial system is largely concentrated in the spleen, the lymph nodes and the bone marrow, and since it gives rise to both macrophages and antibodies (including opsonins, which mediate phagocytosis), it is not surprising that in a state of generalized hypersensitivity, phagocytosis of cellular debris should be active and readily noted near foci of necrosis in these organs.

The same phenomenon, involving whole erythrocytes and leukocytes in distant, non-necrotic areas is less easily explained. To assume arbitrarily that these corpuscles are physically damaged does not appear warranted. Neither does the anthropomorphic concept of a "reticuloendothelial system gone wild" offer a sounder explanation. Much more consonant with present day concepts may be the theory that the leukophagocytosis and the erythrophagocytosis represent a form of "foreign body reaction" in which the homologous blood cells are so changed by the addition of a substance (perhaps a conjugated sulfonamide group) as to render them alien to the protein pattern of the patient. Such a change may conceivably convert the erythrocytes or the leukocytes into allergens capable of eliciting the production of specific antibodies. Dameshek,[34] indeed, suggested that this mechanism was the probable method of production of the "cold hemagglutinins" which are a factor in the hemolytic anemia that sometimes follows treatment with sulfonamide compounds.

It appears that agranulocytosis and leukopenia, both of which may complicate the therapeutic use of sulfonamide compounds, may represent the analogue of hemolytic anemia. This concept finds support in experimental literature as well as in clinical experience. Chew[35] and co-workers produced in guinea pigs by means of leukotoxic serums not merely marked leukopenia but definite neutropenic states comparable to agranulocytosis. The antibodies causing neutrophils to disappear from the blood were obtained in exactly the same manner in which hemolysins are ordinarily produced: by inoculating leukocytes into an animal of a "foreign" species (rabbit).

28. Longcope, W. T.: J. Exper. Med. **22**:793, 1915. Heinlein.[23a] Klinge.[23b] Vaubel.[23c] Apitz.[23d]

29. Clark, E., and Kaplan, B. J.: Arch. Path. **24**: 458, 1937.

30. Schmeisser, H. C., and Harris, L. C.: Am. J. Path. **14**:821, 1938.

31. Enzer, N.: Am. J. Path. **2**:511, 1926.

32. Magnus, H. A.: J. Path. & Bact. **44**:103, 1937.

33. Lederer and Rosenblatt.[17] Merkel and Crawford.[18] Rich.[19]

34. Dameshek, W.: J. A. M. A. **123**:77, 1943.

35. Chew, W. B.; Stephens, D. J., and Lawrence, J. S.: J. Immunol. **30**:301, 1936.

Dameshek and Colmes [36] were able to reproduce agranulocytosis with minimal doses of aminopyrine (5 mg. in their case 1) in persons in whom the condition had previously developed during medication with aminopyrine. Furthermore, they obtained positive intradermal reactions to aminopyrine incubated with human serum (conjugation) after failing with aqueous solutions of the pure chemical. Many reports of cases in which agranulocytosis followed treatment with sulfonamide compounds [37] demonstrate that in previously untreated persons the lesion appears shortly after the inception of the syndrome of serum sickness, when antibodies first become demonstrable experimentally.

It is certainly not inconsistent with the facts to state that the concepts of direct toxic chemical depression of marrow activity and "inhibition of maturation" [38] are at the very least, open to objections just as grave as any that may be directed against the anaphylactic concept of agranulocytosis. The combination of the two factors (anaphylaxis and selective chemical toxicity of the marrow) presents a more satisfactory approach to the problem of both leukopenia and agranulocytosis.

In the 5 cases the liver showed little individual variation. In no instance was widespread necrosis such as characterizes acute yellow atrophy seen, nor, for that matter, the aseptic necrobiotic foci said to be especially numerous in this organ in reactions to sulfonamide compounds. On the other hand, all the changes described by Rössle and Eppinger [39] as peculiar to serous hepatitis were demonstrable (fig. 1). The parenchymal trabeculae in most cases were fragmented; the cell cytoplasm was granular. Disse's spaces and Kupffer cells were prominent. Present within the sinusoids and portal fields was an exudate consisting of the same cellular elements so often described in other sites. Within some of the portal fields, small hepatic arteries reflected the generalized vascularitis, and the connective tissue showed the fibrinoid necrosis so typical of reactions to sulfonamide drugs.

Rössle and Eppinger in the course of their separate investigations of hepatic disease described what they called (hepatosis) serous hepatitis. The lesion in its earliest form is similar to that seen in case 3. The chief morphologic change is the appearance of the normally invisible Disse's spaces, which lie between the endothelium of the sinusoids and the liver cells. The phanerosis of these spaces is said to be due to the circumstance that fluid has been lost from the sinusoids because of increased permeability of their lining membrane, as in any inflammatory lesion, and has accumulated within the spaces. This interferes with the nutrition of the cells, and if the process is not reversed, the liver cords dissociate (case 5), sometimes producing jaundice; should the process continue, hepatic necrosis, varying from foci to acute yellow atrophy, may appear. Serous hepatitis is not a pathognomonic lesion but an expression of increased vascular permeability; in this respect the hepatic changes may be likened (just as the early arterial lesions were) to the edematous wheal of cutaneous allergy.

Observations on the kidneys occupy a prominent position in the literature of fatal reactions to sulfonamide drugs since progressive uremia is so frequent a symptom. In 3 cases of the present series the kidneys showed typical focal interstitial round cell exudates, avascular glomeruli, interstitial edema and marked cloudy swelling of the tubular epithelium. In addition to these lesions, the kidneys in case 2 showed isolated convoluted tubules that were necrotic (fig. 5) and some surrounded by a scant neutrophilic exudate.

Multiple foci of well advanced necrosis of the convoluted tubules unaccompanied by interstitial exudate were seen in case 5. The remaining epithelium was swollen, granular and obviously on its way to sharing the fate of that at the sites of the more advanced lesions. This is the only unequivocal example of nephrosis in the series—a reversal of the usual ratio of nephrosis to interstitial nephritis in previous reports.

Kimmelstiel [40] comprehensively reviewed the literature of human interstitial nephritis. One of his conclusions was: ". . . interstitial nephritis is regarded as an allergic hyperergic reaction to foreign proteins or protein split products. . . ." Certainly interstitial nephritis is a common renal lesion in experimental anaphylaxis.[41]

That the nephrosis so frequently reported in reactions to sulfonamide drugs may represent a form of hyperergia and not direct chemical irritation is indicated by the fact that renal

36. Dameshek, W., and Colmes, A.: J. Clin. Investigation **15**:85, 1936.

37. Shecket, H. A., and Price, A. E.: J. A. M. A. **112**:823, 1939. Briggs, G. O. A.: Lancet **2**:739, 1939. Arrowsmith, W. R.; Binkley, B., and Moore, C. V.: Ann. Int. Med. **21**:323, 1944.

38. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Am. J. M. Sc. **188**:104, 1932.

39. Rössle and Eppinger, cited by Eppinger, H.: Die Leberkrankheiten, Berlin, Julius Springer, 1937.

40. Kimmelstiel, P.: Am. J. Path. **14**:737, 1938.

41. Longcope, W. T.: J. Exper. Med. **18**:678, 1913. Heinlein,[23a] Klinge,[23b] Vaubel,[23c]

involvement frequently appears synchronously with, or following, the cutaneous rash (case 5), evidence of antigen-antibody reaction in other tissues. Furthermore, in case 5 uremia manifested itself only during the second reaction, at a time when it may be surmised that sensitivity to sulfanilamide had increased. In many instances of nephrosis demonstrated to be due to therapy with a sulfonamide compound, the amount of drug used was so small as to exclude as unreasonable any explanation other than that of anaphylaxis.

Rackemann, Longcope and Peters [42] investigated the clinical significance of the edema of serum sickness and concluded that it, as well as oliguria (which, they stated, may progress to urinary suppression), is due to damage of the kidney. The nature of the lesion was not investigated.

The pancreatitis in case 3 is an unusual lesion. Rich [20] mentioned without further comment a similar pancreatitis in a case in his series. The cause is suggested in the focal fibrinoid necrosis of the small arteries and in the identity of the exudate with that demonstrated at other sites. Nonhemorrhagic interstitial pancreatitis is an unsolved problem; certainly the lesions in case 3 and in the case of Rich indicate that one of the etiologic mechanisms may be anaphylaxis.

Rich [20] described the underlying pulmonary lesion in the same case in which the pancreatitis was observed as capillaritis with interalveolar exudation. Rich and Gregory [43] and also Pinkerton [44] elaborated on the appearance of this peculiar pneumonitis, emphasizing the vascular necrosis and the subsequent interalveolar infiltration as well as the appearance of a fibrin membrane outlining the alveolar walls. Where the stimulation was sufficiently powerful, necrosis occurred. Gessler [24] noted the same lesion in his case 1.

The lungs in my cases 2 and 3 showed similar lesions (fig. 3). Rich and Gregory,[43] furthermore, compared the pneumonitis which they observed to that encountered in 5 patients with rheumatic heart disease; the processes were identical, and since the pulmonary lesions following administration of sulfonamide compounds are the reflection of a pulmonary anaphylactic reaction, they concluded that this form of rheumatic pneumonia was added evidence of the allergic nature of rheumatic fever.

The experimental work of Cannon, Walsh and Marshall [45] resulted in the production of anaphylactic pneumonia, which was described as acute pneumonitis characterized by edema, alveolitis, bronchitis and focal pneumonic consolidation. Acute arteritis and phlebitis occurred at times, and mural thrombosis was occasionally encountered.

While convincing experimental evidence of the morphologic nature of anaphylactic pneumonia is lacking, the evidence at hand would indicate that it is essentially an interstitial process (interstitial pneumonitis).

In case 2 the aorta presented a unique lesion. Acute thromboaortitis produced in man in the course of reactions to sulfonamide compounds has never been described. Lehr and Antopol [46] did observe medial necrosis and calcification of the thoracic aorta in rats given a large single dose of sodium sulfadiazine. Junghans (quoted by Heinlein [23a]) examined the aortas of rabbits sensitized to hog serum and found in each mucoid degeneration of the thickened intima, which was infiltrated by monocytes up to and including the innermost medial muscle fibers.

Seegal, Seegal and Jost,[47] using rabbits, produced a local Arthus reaction within the pericardial sac. They observed intimal thickening and subendothelial polymorphonuclear leukocytic exudate of the aorta.

The thromboaortitis in case 2 represented in its pattern the same type of reaction as the process seen in the smaller arteries.

Available evidence does not permit any conclusions concerning the nature of the lesion. The suggestion is advanced, however, that in view of the generalized nature of the reaction that sometimes follows treatment with sulfonamide compounds and the fact that Junghans did demonstrate hyperergic aortitis in rabbits, the thromboaortitis may be the result of an anaphylactic reaction.

It is obvious that more questions are suggested than are answered by the preceding exposition; however, the protean nature of generalized anaphylaxis is indicated.

The sulfonamide drugs were administered in all cases except case 2 for some underlying disease, which may have contributed to the lesions observed. This possibility should not lightly be brushed aside; yet numerous authors have inde-

42. Rackemann, F. M.; Longcope, W. T., and Peters, J. P.: Arch. Int. Med. **18**:496, 1916.

43. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **73**:465, 1943.

44. Pinkerton, H.: J. Missouri M. A. **40**:364, 1943.

45. Cannon, P. R.; Walsh, T. E., and Marshall, C. E.: Am. J. Path. **17**:777, 1941.

46. Lehr, D., and Antopol, W.: Urol. & Cutan. Rev. **45**:545, 1941.

47. Seegal, D.; Seegal, B. C., and Jost, E. L.: J. Exper. Med. **55**:155, 1932.

pendently recorded the same lesions in various unrelated disease states in which the only common factor was the administration of sulfonamide compounds.

The identity of the lesions with those produced in a few human subjects and many animals by known species-foreign proteins, the knowledge that the sulfonamide compounds may convert homologous proteins into allergens and the fact that characteristic clinical syndromes follow the administration of the drugs constitute sufficient evidence to justify the concept of the anaphylactic nature of the lesions described.

SUMMARY

The relatively large number of deaths accompanying the universal use of sulfonamide drugs has made possible for the first time a systematic study of progressive fatal human anaphylaxis from the standpoint of pathology.

The basic lesion, as in experimental protein anaphylaxis, is necrotizing fibrinoid arteritis of the smaller vessels. The cellular exudate is monocytic in composition. The reticuloendothelial system is hyperplastic; in the spleen, the lymph nodes and the marrow the sinusoids may be crowded with macrophages showing phagocytosis of erythrocytes and leukocytes.

It is suggested that this phenomenon may be the morphologic expression of the addition of some substance to the blood cells (conjugated sulfonamide group?) that renders them "foreign." The possibility that these homologous "foreign cells" may elicit the production of antibodies is suggested and may account for the hemolytic anemia, the leukopenia and the agranulocytosis.

The available evidence indicates, it is believed, that the nephrosis in cases of reaction to treatment with sulfonamide compounds is a form of anaphylactic renal reaction.

PRIMARY SYSTEMIC AMYLOIDOSIS

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Primary systemic amyloidosis is a rare disease of unknown cause. It differs from the more common secondary amyloidosis in several respects: (*a*) the absence of specific etiologic factors, such as tuberculosis or chronic suppuration; (*b*) the minimal deposition of amyloid in the liver, the spleen, the kidneys and the adrenal glands, the sites of maximum deposition in the secondary type of amyloid disease; (*c*) the maximum deposition of amyloid in the heart, the lungs, the skin, the mucous membranes and other tissues not usually involved in the secondary type; (*d*) the occasional occurrence of amyloid tumors; (*e*) the atypical reactions with specific amyloid stains.[1]

To date 39 cases of primary systemic amyloidosis have been recorded. Koletsky and Stecher [2] collected 23 cases reported in the literature up to 1939, and added a case of their own. Their report included an extensive tabulation of the clinical and pathologic changes noted in these cases. Additional reports published before 1939 include those of Beneke and Bönning,[3] Silwer and Lindblom,[4] Larsen,[5] Koller,[6] Israel,[7] Gerber [8] and Kerwin.[9] Since 1939 cases have been reported by Binford,[10] Pearson, Rice and Dickens,[11] Sappington, Davie and Horneff [12] and Dillon and Evans.[13] These additional cases, together with our own case, are summarized in the accompanying table.

The additional example of primary systemic amyloidosis which we record presented an unusual combination of pathologic changes. The diagnosis was not made until after death although biopsy specimens from the external ear and the nasal mucosa both contained unrecognized deposits of amyloid.

REPORT OF A CASE

P. B., a 56 year old Frenchman, entered the Mills Memorial Hospital in San Mateo, Calif., Oct. 9, 1936, complaining of redness, swelling and pain over the right thenar eminence following a superficial abrasion of the skin. An abscess was incised and drained, with the patient under general anesthesia. His temperature on entry was 104 F. It promptly returned to normal after the operation. The postoperative course was uneventful.

He entered the hospital again on Jan. 22, 1941, with a three day history of pain in and purulent drainage from the right ear. Sagging of the posterior wall of the right external acoustic meatus and perforation of the right tympanic membrane were noted. A roentgenogram showed mastoiditis on the right side.

At this time the hemoglobin was 90 per cent (13.05 Gm.), the red cell count 4,080,000 and the white cell count 17,450, with polymorphonuclear leukocytes 40 per cent (nonsegmented 4 per cent), lymphocytes 59 per cent and monocytes 1 per cent. The urine was normal. January 24 the white blood cell count was 12,900, with polymorphonuclear leukocytes 37 per cent (7 per cent nonsegmented), large lymphocytes 3 per cent, small lymphocytes 58 per cent and monocytes 2 per cent.

Mastoidectomy was done on the right side, and a large amount of purulent material and necrotic mastoid cells were encountered. His postoperative course was uneventful and afrebrile. He was given sulfathiazole, 7 Gm. the first twenty-four hours and 4 Gm. every twenty-four hours for the next three days. The eustachian tubes were inflated on several occasions during the next two months.

The patient again entered the clinic, Jan. 19, 1942, with the complaints of (*a*) pain in the thoracic part of the spine, aggravated by movement, coughing or jarring, (*b*) loss of 15 pounds (6.5 Kg.), (*c*) bilateral nasal obstruction, (*d*) nasal bleeding of about 500 cc. per month and (*e*) epigastric pain beginning two hours after meals and relieved by alkalis taken before and

From the Division of Pathology, University of California Medical School, San Francisco, and Mills Memorial Hospital, San Mateo.

1. Lubarsch, O.: Virchows Arch. f. path. Anat. **271**:867, 1929.
2. Koletsky, S., and Stecher, R. M.: Arch. Path. **27**:267, 1939.
3. Beneke, R., and Bönning, F.: Beitr. z. path. Anat. u. z. allg. Path. **44**:362, 1908; cited by Larsen [5] and by Binford.[10]
4. Silwer, H., and Lindblom, A. D.: Acta med. Scandinav. **64**:529, 1926.
5. Larsen, R. M.: Am. J. Path. **6**:147, 1930.
6. Koller, F.: Schweiz. med. Wchnschr. **13**:522, 1932.
7. Israel, I.: Ein Fall von lokalen Amyloid, Med. Dissert., Tübingen, Bochum-Langendreer, 1933; cited by Koletsky and Stecher [2] and by Spain and Barrett.[20]
8. Gerber, I. E.: Arch. Path. **17**:620, 1934.
9. Kerwin, A. J.: J. Lab. & Clin. Med. **22**:255, 1936.
10. Binford, C. H.: Arch. Path. **29**:314, 1940.
11. Pearson, B.; Rice, M. M., and Dickens, K. LaV.: Arch. Path. **32**:1, 1941.
12. Sappington, S. W.; Davie, J. H., and Horneff, J. A.: J. Lab. & Clin. Med. **27**:882, 1942.
13. Dillon, J. A., and Evans, L. R.: Ann. Int. Med. **17**:722, 1942.

Summary of Cases Recorded in the Literature (in Addition to Those Tabulated by Koletsky and Stecher [2])

Author	Year	Age	Sex	Symptoms	Clinical Diagnoses	Duration	Cause of Death	Distribution of Amyloid
Beneke and Bönning [3]	1908	70	M	Not known	Bronchitis	Not known	Not known	Heart, vena cava, lungs
Silwer and Lindblom [4]	1926	34	M	Dyspnea, weakness, edema of legs, cyanosis, mental depression	Myocardial insufficiency	11 mo.	Cardiac failure	Myocardium, mitral valve, arteries of heart, liver, spleen, kidneys and lungs
Larsen [5]	1930	65	M Negro	Cough, dyspnea, epigastric tenderness	Coronary arteriosclerosis with cardiac insufficiency	1 yr.	Myocardial failure, streptococcic meningitis and septicemia	Myocardium, endocardium, pulmonary artery, aorta, vena cava, lungs, kidneys, pararenal ganglion
Koller [6]	1932	50	F	Dyspnea, edema of legs	Myocardial insufficiency, ? coronary sclerosis and diabetes	4 mo.	Cardiac failure	Mitral and tricuspid valves, vena cava, tongue, myocardium, arteries of lungs, heart, liver, pancreas and bone marrow
Israel [7]	1933	..	..	Data not available	Data not available	.....	.....	Mitral, tricuspid and pulmonic valves, heart, mouth, larynx, skin, mediastium
Gerber [8]	1934	44	M	Pruritus, postprandial pyrosis, vague muscular pains, weakness	Amyloidosis, amyloid nephrosis, hypercholesteremia, lipoid histiocytosis	2 yr.	Azotemia, pulmonary edema	Diffuse amyloidosis of marrow; amyloidosis of kidney, liver, spleen, pancreas, stomach, thyroid and adrenal glands
Kerwin [9]	1931	51	F	Fatigue, weakness, loss of weight	Chronic degenerative myocarditis	1 yr.	Cardiac failure	Cardiac valves, myocardium, endocardium, pleura, pericardium, lung, stomach, large and small bowel, bladder
Kerwin [9]	1936	59	F	Peripheral edema, dyspnea	Chronic degenerative myocarditis, myocardial insufficiency	4 mo.	Cardiac failure	Myocardium, aortic valves, pericardium, endocardium, liver, spleen, kidneys, adrenal glands
Binford [10]	1940	56	M	Progressive dyspnea	Myocardial degeneration	15 mo.	Myocardial failure	Myocardium, vessels of following: lungs, liver, kidney, adrenal glands, bladder, prostate, seminal vesicles, spleen, pancreas, tracheobronchial lymph nodes, thyroid gland, diaphragm, femoral nerve
Pearson and others [11]	1941	69	F Negro	Dyspnea, edema, papular lesions of mouth and tongue, purpura	Congestive heart failure	3 yr.	Cardiac failure	Heart, lungs, esophagus, stomach, small intestines, spleen, vessels of thyroid gland
Pearson and others [11]	1941	60	M Negro	Hoarseness, cough, hemoptysis, dyspnea, edema of ankles	Amyloid disease	10 mo.	Laryngeal obstruction	Pharynx, larynx, trachea, esophagus, stomach, diaphragm, subcutaneous tissues, peritracheal and peribronchial tissues, great vessels, auricles of heart, capsules of adrenal glands
Sappington and others [12]	1942	51	F	Fatigue, dyspnea, distress in upper part of abdomen	Not stated	3 yr.	Not stated; sudden death	Lungs, skin, systemic involvement of small and medium size arteries
Dillon and Evans [13]	1942	61	M	Radiating substernal pain and dyspnea, loss of weight, purpura	Myocardial infarction, malignant lymphoma	6 mo.	Cardiac failure	Liver, spleen, kidneys, blood vessels of all organs except spinal cord, including heart
Dillon and Evans [13]	1942	57	F	Constipation, loss of weight, fatigue	Chronic nephritis, amyloidosis, rheumatic heart disease, possible subacute bacterial endocarditis	2 yr.	Hyperpyrexia, cardiac failure, subacute bacterial endocarditis	Spleen, liver, heart, brain, parathyroid glands, stomach, colon, adrenal glands, kidneys
Dillon and Evans [13]	1942	52	M	Peripheral edema, pains and paralysis of leg	Chronic nephritis with edema (nephrosis), phlebitis of right leg	3 yr.	Terminal pneumonia	Kidneys, spleen, liver, adrenal glands
Lindsay and Knorp	1945	60	M	Pain in thoracic part of spine, loss of weight, nasal obstruction and hemorrhage, epigastric and substernal pain, orthopnea and dyspnea	Gastric ulcer, coronary atherosclerosis with cardiac insufficiency	20 mo.	Acute cardiac failure, myocardial infarction	Skin of ears, fingers and toes, endocardium and cardiac valves, pulmonary artery, gastric mucosa, aorta, lymph nodes, bone marrow, nasal mucosa, adrenal glands, liver, spleen, pancreas, arteries and arterioles of pancreas, spleen, kidney, testes and stomach

after eating. These symptoms had been noted for approximately one year. He had been unable to continue his occupation as a carpenter because of the pain in his back. His family and past history were not significant, though he stated he had never felt well since the infection of the hand five years before.

The patient was a 60 year old man, weighing 134 pounds (60.5 Kg.). His temperature was 98.4 F.; his pulse rate, 74. A perforation of the anterior portion of the nasal cartilage was surrounded by abundant, soft, pale, pink polypoid tissue, which was producing bilateral nasal obstruction. The mouth, the tongue, the pharynx and the larynx were normal. The jaws were edentulous. On the superior surface of the helix of each ear was an irregularly outlined moist red eczematous lesion, 1 cm. in diameter. The nasal and aural lesions were submitted to biopsy and will be described on later pages. The external lymph nodes and the thyroid gland were not enlarged. There was marked thoracic kyphosis centering between the third and fifth dorsal vertebrae. The anterior-posterior and transverse diameters of the chest were equal.

The diaphragms moved well. The lung fields were clear. The heart was normal in size; the rhythm was regular, and the sounds were of good quality; no murmurs were heard. The blood pressure was 130 systolic and 80 diastolic. The abdomen, the rectum and the genitalia revealed nothing significant. Narrow dark pink longitudinal striations were seen beneath the nails of the fingers and the toes. The urine was normal. The Kline test was negative. Analysis of the gastric content gave values within normal limits.

Roentgen examination showed a large ulcer on the upper lesser curvature of the stomach. By fluoroscopy no peristaltic waves were noted in the gastric wall in the region of the ulcer. There was moderate diffuse osteoporosis of the thorax and the pelvis with accentuation of the trabecular markings. The thoracic vertebral bodies were narrowed anteriorly, leading to marked dorsal kyphosis. There was considerable thickening of the anterior intervertebral margins of these bodies.

After three weeks on a dietary regimen the patient was greatly relieved subjectively. The gastric ulcer was one quarter of the former size in subsequent roentgenograms.

At this time, however, the patient first complained of oppressive substernal pain with radiation down both arms. The occurrence of numerous similar attacks in the past was brought out by further questioning. The pain occurred during the day and was associated with considerable orthopnea and dyspnea. An electrocardiogram on April 1, 1942 showed a rate of 60 per minute, regular rhythm, upright P waves, a normal PR interval, slightly slurred QRS, slightly high ST segments in I and II, essentially flat ones in III and IV and upright T waves. This was interpreted as minimal evidence of myocardial damage.

On April 13 he entered the hospital complaining of pain in the left side of the chest, increased with respiration and associated with an elevated temperature, malaise, cough and hemoptysis of a week's duration. Examination showed an ill elderly man, coughing at intervals and expectorating blood-streaked sputum. His temperature was 102 F. The nasal mucosa showed the same changes that were noted previously. There was redness of the pharynx. The lymph nodes were not enlarged. Dulness and diminished breath sounds were present over the lower lobe of the left lung. Coarse rhonchi were heard posteriorly over the lower lobe of the right lung. The heart was centrally placed and normal in size; the rhythm was regular, and the rate was 95.

A roentgenogram showed an area of infiltration in the lower half of the lower lobe of the left lung. The bronchovesicular markings were slightly accentuated.

The urine contained the faintest possible trace of albumin. The white blood cell count was 25,800, with polymorphonuclears 47 per cent (12 per cent nonsegmented), lymphocytes 50 per cent and monocytes 3 per cent. A diagnosis of acute bronchitis with bronchopneumonia and atelectasis of the lower lobe of the left lung was made. Sulfathiazole was administered, 1 Gm. every four hours for four days and 1 Gm. every eight hours for four days. His temperature returned to normal on the third day after entry, and except for a rise to 100 F. on the sixth day, remained normal thereafter. During his hospital stay he had frequent attacks of intense boring substernal pain, not aggravated by movement but relieved by glyceryl trinitrate. On several occasions the urine showed a faint trace of albumin and numerous sulfathiazole crystals. The white blood cell count gradually decreased to 8,500, with polymorphonuclears 31 per cent (2 per cent nonsegmented), lymphocytes 65 per cent and monocytes 4 per cent. His red blood cell count remained low (3,200,000), with hemoglobin 78 per cent. He remained in the hospital for twenty-eight days.

He again entered the clinic, May 17, 1942, with a history of nausea, vomiting and diarrhea of three days' duration. He had lost weight and was obviously ill. There were no other significant physical findings. The hemoglobin at this time was 60 per cent, but there was no blood in his stools. Rest in bed and continuation of the dietary regimen were advised.

By June 2 he had been relieved of his abdominal distress, though he still had an occasional episode of radiating pain in the chest. These attacks occurred particularly at night but also followed exertion during the day. The general condition appeared to be improved; the weight had increased, the heart and the lungs were normal and the blood pressure was 140 systolic and 85 diastolic.

On July 8 he stated that his gastric distress had recurred but that the episodes of thoracic pain had diminished in severity.

On August 10 marked malaise and dyspnea developed. The skin had a yellowish tinge, and enlarged bilateral cervical lymph nodes were palpable. Moist rales were heard in both lungs. The apical beat was felt in the left fifth intercostal space. A systolic murmur was heard over the entire precordium but was heard best at the apex. An occasional ectopic beat was noted. The right upper quadrant of the abdomen was tender. The edge of the liver was felt 6 to 7 cm. below the right costal margin. The spleen was enlarged to 1 cm. below the left costal margin. Because his condition did not improve at home, he was advised to enter the hospital.

On his last entry, August 15, his condition was unchanged. His pulse was thready and irregular, with a rate of 120. His respiratory rate was between 32 and 36. He was expectorating sanguineous yellowish sputum. The tongue was dry and coated. Fine moist rales were heard in both lungs. The apical beat was felt in the left fifth intercostal space, outside the left sternoclavicular line. A systolic murmur was heard at the apex over the aortic area. His temperature was 101 F. on entry and remained above 100 F. during his stay in the hospital. There was no response to digitalis, nickethamide or digifolin or to sedatives. Death occurred thirty-six hours after entry.

Autopsy (five hours after death).—The lesions of the ears and the nails of the fingers and the toes appeared as before death. External examination revealed no other significant abnormality.

The heart weighed 550 Gm. Its left border extended 11 cm. to the left of the midline and its right border 5 cm. to the right of the midline. The anterior surface of the left ventricle had a dark, congested, mottled appearance though the epicardium was intact. All the chambers of the heart were dilated. The left ventricle had a globular outline. The left ventricular wall averaged 1 cm. in thickness, and its anterior portion showed a diffuse congested mottling with small yellowish opaque zones of early necrosis. Elsewhere the myocardium was normal. The right ventricular wall averaged 0.5 cm. in thickness. The valves measured as follows: aortic, 8 cm.; mitral, 11 cm.; tricuspid, 12 cm; pulmonary, 9 cm.

All the valves and much of the endocardium in all the chambers of the heart showed a remarkable alteration (figs. 1 and 2). Covering a large part of the valve surfaces and extending onto the chordae tendineae and adjacent endocardial surfaces were elevated, confluent nodular masses of smooth, glistening, translucent yellowish white, soft amyloid material. On the left side of the heart this material was most abundant on the under surface of the aortic leaflet of the mitral valve and extended upward beneath and onto the aortic cusps (fig. 1). On the latter most of the deposition was along the free edges and in the commissures. In addition, the aortic cusps were thickened, fibrous and moderately rigid and contained yellow atheromatous deposits in their deeper portions. Smaller nodules and deposits of similar translucent material were present throughout the left ventricular chamber, projecting from the endocardium. Both small and large endocardial plaques were present in the left auricle. On the right side of the heart the valvular alteration was even more extensive. Both on the tricuspid and on the pulmonary valve (fig. 2) the translucent deposits were more elevated and more nodular and covered more of the valvular surfaces. Deposits on the chordae tendineae had marked nodularity. In these situations the fibrous structure of the chordae tendineae was visible through the overlying translucent amyloid layer. This material extended distally from both the aortic and the pulmonary valve to involve the intima of the aorta and that of the pulmonary artery (fig. 3). The involvement of the latter was greater. There were small nodular amyloid deposits in the endocardium of the right auricle and ventricle. There was marked atherosclerosis of the right and left coronary arteries with narrowing of the lumen of each vessel. Complete obstruction could not be demonstrated.

Atherosclerosis of the aorta with ulceration and calcification was most marked in the arch and in the abdominal portion. In addition there was extensive intimal deposition of glistening pale gelatinous material in all portions of the aorta. The vena cava was normal.

The pericardial cavity was normal. There was 1,500 cc. of clear yellow fluid in the right pleural cavity, 500 cc. of similar fluid in the left pleural cavity and 1,500 cc. in the abdominal cavity.

The larynx, the thyroid gland, the trachea and the bronchi were not altered. The extensive confluent nodular intimal deposits in the pulmonary artery extended well down into the smaller branches of the pulmonary artery. Both lungs were congested and moderately edematous. In each lower lobe were several small triangular-shaped dark red firm subpleural infarcts.

The liver weighed 2,200 Gm. and extended 4 cm. below the xiphoid process and the right costal margin. The anterior edges were rounded. The parenchyma was pale with marked central congestion. The gallbladder wall was edematous. The spleen was enlarged and weighed 680 Gm. The pulp was soft, hyperplastic and light purple.

The adrenal glands, the kidneys, the renal pelves, the ureters, the bladder, the prostate gland and the testes were normal.

The gastroenteric tract was normal except for the stomach. On the lesser curvature, 4 cm. from the cardioesophageal junction, was a large ulcer, measuring 4 by 5 cm. in diameter (fig. 4). Its edges were elevated, sloping and indurated. Abundant glistening yellowish white soft gelatinous amyloid material lined the crater. Perforation had occurred, extending through almost the entire wall. The serosal surface was scarred and contracted.

A group of enlarged, amyloid-containing lymph nodes, forming a mass measuring 12 cm. in diameter, lay just above the head of the pancreas (fig. 5). Strong solution of iodine U. S. P. stained the amyloid material in these nodes light brown. Similar but smaller nodes lay along the lesser curvature of the stomach and along the abdominal portion of the aorta.

The mesentery of the small bowel was thickened and its surface mottled and congested. Tending to surround the mesenteric lymph nodes were rounded zones of opaque, yellowish white fat necrosis. The larger mesenteric arteries had small intimal deposits of pale, translucent amyloid material.

The marrow space of the medial portion of the clavicle consisted entirely of amyloid material.

The spine and the cranial cavity were not examined.

After several days' fixation in a solution of formaldehyde the amyloid material in all the tissues underwent considerable shrinkage and took on a brownish purple color but retained its glistening translucent characteristics.

Microscopic Description.—The pericardial fat contained many small collections of lymphocytes, plasma cells and large mononuclear cells. There was considerable interstitial myocardial edema. Some groups of myocardial fibers had been replaced by a cellular fibrous tissue, while other groups within the left ventricle were necrotic and surrounded by neutrophilic leukocytes. The endothelium of the ventricles and valves was intact. The subendothelial layer was widened, contained an unusually rich network of reticulum fibers and consisted of eosinophilic amorphous homogeneous material in which there were scattered compressed fibrocytes. The connective tissue fibers, demonstrated with the Mallory and Laidlaw connective tissue stains, separated the amyloid into irregular rounded masses. There were no myocardial or pericardial amyloid deposits.

All the heart valves presented an identical histologic appearance (fig. 7). Lying between the intact endothelium and the central fibrous portion of the valve was a wide layer of eosinophilic amorphous homogeneous amyloid material containing scattered compressed fibrocytes. As in the endocardium, this material was well supplied with reticulum and collagen fibers. There was no increased vascularity of the valves. A minimal lymphocytic infiltration was present in the deeper areas. The distal portions showed more extensive deposits than the proximal portions. The

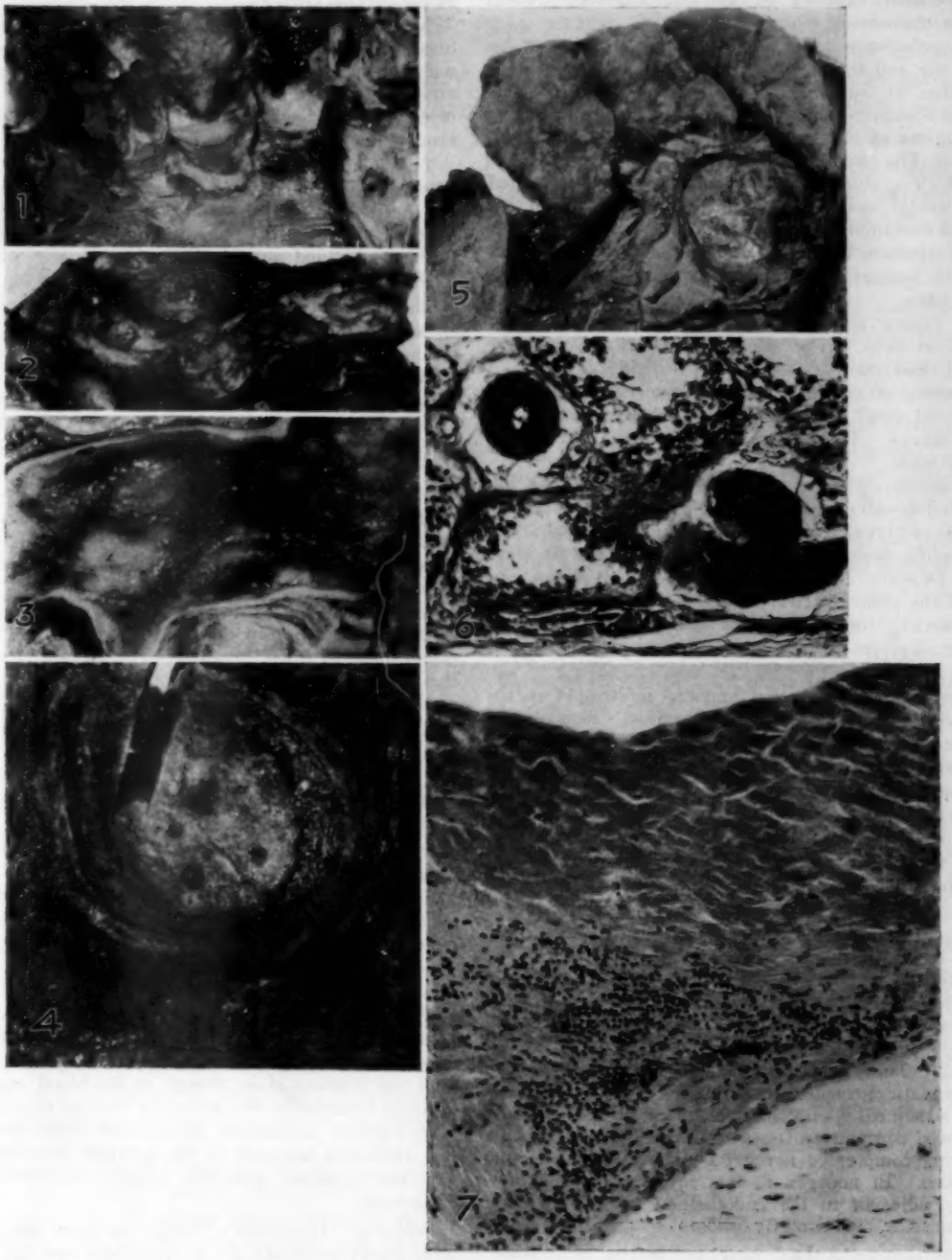

Fig. 1.—Left ventricle showing deposits of amyloid in the aortic and mitral valves; × 0.6.
Fig. 2.—Pulmonary valve with extensive deposits of amyloid; × 0.6.
Fig. 3.—Pulmonary artery showing extensive deposits of amyloid in the intima; × 1.1.
Fig. 4.—Gastric ulcer with amyloid material visible in the crater of the ulcer; × 1.
Fig. 5.—Peripancreatic lymph nodes with extensive deposits of amyloid; × 0.7.
Fig. 6.—Small testicular arteries with amyloid infiltration; hematoxylin and eosin stain; × 120.
Fig. 7.—Subendothelial amyloid infiltration of a cardiac valve; hematoxylin and eosin stain; × 120.

small myocardial arteries were not altered. The large coronary arteries showed extensive intimal atherosclerosis with marked narrowing of the lumens. Contributing in a small degree to this narrowing were subendothelial deposits of amyloid material. There was no thrombosis.

The pulmonary artery and its branches showed between the endothelium and the media a wide zone of deposition of amyloid. This contained a few compressed fibrocytes and small collections of lymphocytes. The lumens of the involved smaller vessels were narrowed. The smallest pulmonary arteries were not altered. The alveolar walls were fibrous and congested. The alveolar spaces contained serous fluid, fibrin and pigment-containing macrophages. There was no inflammatory reaction and no deposition of amyloid. Zones of early hemorrhagic infarction were present in the lower lobes.

The hepatic sinusoids were wide but contained few red blood cells. The parenchymal cells were compressed, and many contained small lipid globules. A few groups of central cells were undergoing necrosis. Occasional small deposits of amyloid were present in portal spaces. There was marked edema of the gallbladder wall.

The spleen contained numerous large malpighian follicles. The pulp was cellular and consisted almost entirely of lymphocytes and reticuloendothelial cells. Neutrophilic leukocytes were present in moderate numbers. Deposits of amyloid were seen in about one half of the central arterioles. They were most abundant beneath the endothelium and in the adventitia. Smaller deposits of amyloid were noted beneath the splenic capsule.

There was subendothelial amyloid infiltration in the large and the small pancreatic arteries. Beneath the amyloid layer were large atheromatous deposits. The pancreatic parenchyma was not altered except for an occasional small amyloid mass in the interstitial tissues with no apparent relation to blood vessels.

The renal parenchyma was not significantly altered except for small deposits of amyloid in a few afferent arterioles.

The bladder and the prostate gland were not altered.

In the testes were many altered blood vessels consisting of an inner layer of endothelium, a wide zone of amyloid material and a thin adventitial layer (fig. 6). A moderate degree of spermatogenesis was noted, and the interstitial cells were normal.

All the lymph nodes examined contained deposits of amyloid. These were particularly extensive in the peripancreatic group of nodes, where little lymphatic tissue remained. The amyloid material was present as rounded concentric masses separated by narrow clefts containing compressed fibrocytes and small lymphocytic collections. In nodes with less involvement the amyloid lay adjacent to the endothelium of blood vessels and sinusoids, particularly those of the subcapsular group.

The small and the large bowel were normal. The gastric mucosa was thin and atrophic. The few remaining gastric glands were irregularly arranged and were separated by many lymphocytic collections and masses of amyloid material. At the edge of the gastric ulcer the mucosa was thicker but still retained its disorganized structure. There was no epithelium in the crater of the ulcer. The gastric wall beneath was extensively infiltrated with amyloid material. This lay in the interstitial tissue, compressed the muscular layers, was deposited in the arterial walls and was accompanied by many lymphocytic collections.

Groups of fat cells in the mesentery of the small bowel were necrotic. These were surrounded by lipid-containing macrophages and lymphocytes.

Small interstitial deposits of amyloid were present in the adrenal cortices.

At various levels the aorta had essentially the same histologic appearance. The intima was irregularly widened by subendothelial amyloid infiltration. The atheromatous lesions present were between the amyloid layer and the media. There were a few lymphocytes around the vasa vasorum.

The acini of the thyroid gland were uniform in size. The central colloid stained more deeply than that at the periphery. In the interstitial tissue were small lymphocytic collections, small groups of lipid-containing macrophages and an occasional foreign body cell. No amyloid was encountered.

The trabeculae in the clavicular marrow were widely separated. The marrow spaces were almost entirely occupied by eosinophilic homogeneous amyloid material. Few myelocytic and erythrocytic elements were present. Megalokaryocytes and plasma cells were absent.

The biopsy specimens from the ear and the nose were reexamined after the patient's death. In both there was extensive deposition of amyloid in the subepithelial tissues.

At those sites where the amyloid material was abundant, it was deposited as rounded concentric masses, separated by compressed fibrocytes, and contained a dense network of reticulum and collagen fibers. In the large arteries, the cardiac valves and the endocardium a uniform relationship to the endothelium could be established. In the small vessels, primarily arterial, the material left no residual mural tissue and led to marked narrowing of the lumens.

A few small arteries showed another type of alteration. These vessels contained no deposits of amyloid but showed distinct edema of the vessel wall with separation of the muscular and the connective tissue elements and exfoliation of the endothelium.

Observations with Special Staining Methods.—Tissues prepared with congo red, crystal violet and Mayer's iodine stains gave variable results when compared with control tissues presenting secondary amyloidosis. In general, the amyloid material stained less deeply and distinctly than that in secondary amyloidosis with all these stains. Of these, the congo red stained the amyloid more deeply. There was considerable variation in staining intensity with the same stains in different tissues. The amyloid material appeared a brilliant red with the Mallory stain, though in the blood vessels the amyloid material at the periphery had an orange color. The Laidlaw connective tissue stain demonstrated a fine reticulum network in the amyloid deposits. This was not apparent with the routine hematoxylin and eosin stain.

Pathologic Diagnosis.—Primary systemic amyloidosis, with involvement of: the endocardium and the cardiac valves; the pulmonary artery and its branches, with multiple pulmonary infarcts; the aorta; the gastric mucosa, with atrophic gastritis and chronic gastric ulcer; the lymph nodes; the bone marrow; the arteries and arterioles of the pancreas, the spleen, the kidneys, the testes and the stomach; the adrenal glands; the liver; the spleen; the pancreas; the skin of the ears, and the nasal mucosa. Generalized arteriosclerosis with aortic and aortic valvular atherosclerosis and coronary atherosclerosis followed by myocardial infarction of the left ventricle with myocardial failure, producing

pulmonary congestion, bilateral hydrothorax, hepatic congestion and ascites. Fat necrosis of the mesentery of the small bowel.

COMMENT

Reimann, Koucky, and Eklund [14] have proposed a simple clinicopathologic classification of amyloid disease: primary amyloidosis, secondary amyloidosis, tumor-forming amyloidosis and amyloidosis associated with multiple myeloma.

The primary form is characterized by (*a*) involvement of the mesodermal tissues, the cardiovascular system, the gastroenteric tract, the smooth and the striated muscle and the lymph nodes, (*b*) little or no involvement of those tissues usually containing deposits of amyloid in the secondary form, (*c*) formation of nodular masses of amyloid, (*d*) deposition of amyloid that shows atypical staining reactions and (*e*) absence of preceding infection.[15]

The secondary form is the most common, follows chronic suppurative disease, is characterized by deposits of amyloid that give a typical reaction to amyloid stains and extensively involves the liver, the spleen, the kidneys and the adrenal glands.

Tumor-forming amyloidosis belongs to the primary type but is characterized by solitary or multiple amyloid tumors in the respiratory tract and other situations.[16]

Amyloidosis occurring with multiple myeloma is characterized by a distribution similar to that seen in the primary type, though large deposits may be found in the joints and elsewhere.[17]

As more cases of all types are recorded, it is apparent that the characteristics of each type merge considerably.[18] In addition, the cases recorded by Budd [19] and Spain and Barrett [20] presented a mesodermal distribution of amyloid, characteristic of the primary type, though the disease occurred secondary to chronic suppuration. In other cases in which there was a mesodermal distribution, the supposed primary inflammatory process may have been coincidental.[21]

The separation of primary isolated amyloidosis and primary systemic amyloidosis seems artificial. While the bulk of the amyloid material may be present in one or two organs, deposits are almost invariably found in other tissues.

The origin of amyloid material in both the primary and the secondary form of amyloidosis remains obscure. Hass and Schulz [22] and Hass [23] have shown that amyloid is composed of two protein fractions and one polysaccharide fraction. It has been suggested that the deposition of amyloid may be the result of a reaction between a component of the serum globulin and fixed tissue elements in the vascular walls, i. e., an antigen-antibody reaction.[2] Amyloid material then may be a precipitate resulting from this union. Presumably this reaction occurs in or on vascular lining cells.[24] Moreover, the relation of amyloid to vascular endothelium is particularly striking both in the primary [6] and in the secondary form of the disease. Because of the overlapping of the four general types of amyloid disease, it is possible that in the future hypersensitivity states other than bacterial may be implicated in the so-called primary type. Sensitivity to drugs or foods may be responsible.

The valvular and endocardial deposits in this case were extensive, particularly on the right side of the heart. The resulting thickening and rigidity undoubtedly contributed in part at least to the cardiac failure. While there were small endothelial deposits of amyloid in the main coronary arteries, the narrowing of these vessels and the subsequent myocardial infarction were the result of atherosclerosis. Although the heart has been the site of deposition of amyloid in most of the cases reported,[2] valvular involvement is usually slight. In the cases described by Wild,[25] Koletsky and Stecher,[2] Silwer and Lindblom,[4] Israel [7] and Koller,[6] however, considerable deposition of amyloid had occurred in the cardiac valves.

The amyloid present in the aorta and the pulmonary artery had the same subendothelial distribution as that in the heart. Where aortic atheromatous lesions were encountered, these lay beneath the amyloid deposits. In Larsen's [5] case the aortic amyloid had a medial distribution, while in the second case described by Pearson, Rice and Dickens [11] the adventitia was the site of maximum deposition.

14. Reimann, H. A.; Koucky, R. F., and Eklund, C. M.: Am. J. Path. **11**:977, 1935.

15. Strauss, A.: Virchows Arch. f. path. Anat. **291**: 219, 1933; cited by Reimann, Koucky and Eklund.[14] Lubarsch.[1]

16. Von Bonsdorff, B.: Finska läk.-sälsk. handl. **75**: 447, 1933; abstracted, J. A. M. A. **101**:489, 1933; cited by Reimann, Koucky and Eklund.[14]

17. Magnus-Levy, A.: Ztschr. f. klin. Med. **126**:62, 1933; cited by Reimann, Koucky and Eklund.[14]

18. Koletsky and Stecher.[2] Reimann and others.[14]

19. Budd, J. W.: Am. J. Path. **10**:299, 1934.

20. Spain, D. M., and Barrett, R. C.: Arch. Path. **38**:203, 1944.

21. Königstein, H.: Arch. f. Dermat. u. Syph. **148**: 330, 1925; cited by Koletsky, and Stecher.[2] Israel.[7]

22. Hass, G., and Schulz, B. Z.: Arch. Path. **30**: 240, 1940.

23. Hass, G.: Arch. Path. **34**:92, 1942.

24. Cannon, P. R.; Walsh, T. E., and Marshall, C. E.: Am. J. Path. **16**:682, 1940.

25. Wild, C.: Beitr. z. path. Anat. u. z. allg. Path. **1**:177, 1886; cited by Koletsky and Stecher.[2]

One of the patient's complaints was severe pain of the back. Narrowing of the thoracic vertebral bodies with resulting kyphosis was probably due to deposition of amyloid in the vertebral marrow.[26] The clavicular marrow was almost entirely replaced by amyloid material. While other portions of the skeleton were not examined, more widespread involvement was likely. The anemia and persistent mild relative leukopenia may have been related to replacement of marrow.

Involvement of the skin was shown in 8 of the 24 cases collected by Koletsky and Stecher.[2] The skin was involved in a case in Pearson's [11] series, and in the cases described by Israel [7] and Sappington and co-workers.[12] The cutaneous lesions are usually nodular or papular and frequently are waxy and translucent. At times they resemble scleroderma. In this case the lesions in the skin were confined to the upper surfaces of the external ears. Each was of the weeping eczematous type. The amyloid was not recognized in the biopsy prior to the autopsy, though the bizarre history and the objective findings suggested that the aural lesion may have been one manifestation of a diffuse process. The nasal amyloid had an identical subepithelial distribution. The longtitudinal striations beneath the nails of the fingers and the toes were not examined histologically but undoubtedly were amyloid in nature.

Amyloid involvement of the oral mucosa, the tongue, the pharynx and the larynx has been described frequently.[2] In this case the amyloid infiltration of the nasal mucosa led to hemorrhage, septal perforation and bilateral nasal obstruction.

The gastroenteric involvement was limited to the stomach. There was resulting mucosal atrophy of the entire organ. The extensive deposition of amyloid in and adjacent to the gastric ulcer indicates an amyloid basis for the ulceration. In a case in Lubarsch's [1] series amyloid disease of the stomach was accompanied by a number of pyloric ulcers, presumably due to deposition of amyloid.

Abundant amyloid infiltration within the peripancreatic group of lymph nodes produced an amyloid tumor. This again demonstrated the merging of the characteristics of the four types of amyloid disease.

26. Mandl, J.: Virchows Arch. f. path. Anat. **253**: 639, 1924; cited by Koletsky and Stecher.[2] Gerber.[8]

SUMMARY

Forty cases of primary systemic amyloidosis have now been recorded in the literature.

In the case of primary systemic amyloidosis recorded in this paper the illness was present for twenty months. There was extensive involvement of the endocardium and of all the cardiac valves, most marked on the tricuspid and pulmonary valves. Abundant amyloid material was also deposited in the skin, the nasal mucosa, the pulmonary arteries, the aorta, the lymph nodes, the stomach and the marrow. Less marked infiltration was present in the adrenal glands, the liver, the spleen, the pancreas and the arteries and arterioles of the stomach, the pancreas, the spleen, the kidneys and the testes. Death resulted from myocardial infarction secondary to coronary atherosclerosis.

PROLIFERATION OF MUSCLE CELLS IN THE MYOMETRIUM OF THE NONPREGNANT UTERUS

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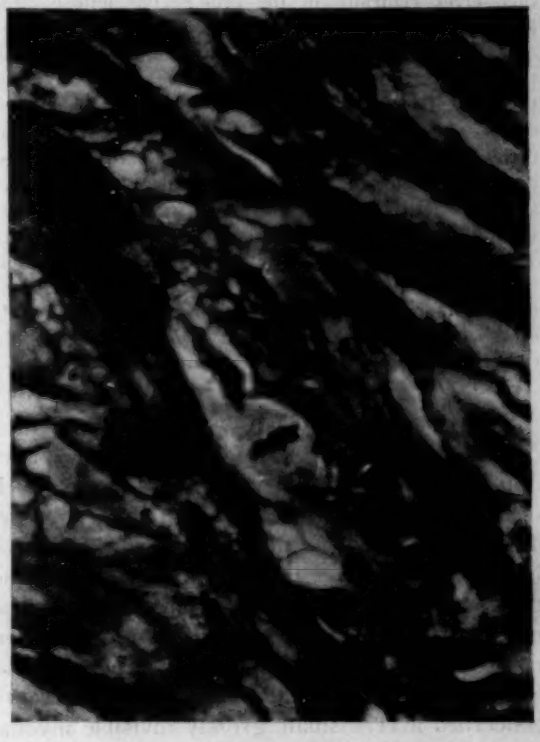
The question whether completely differentiated unstriated muscle cells retain the ability to divide by mitosis is still being discussed. Maximow and Bloom,[1] though admitting that mitosis may occur, expressed the belief that the capacity for regeneration is small. Stieve [2] never observed mitotic division in the muscle cells of the pregnant uterus, and Meyer [3] stated that it is "a generally accepted fact that mitoses do not occur in fully developed muscle cells with myofibrils."

In an article on the mitotic activity in uterine leiomyoma Hartz and Hugenholtz [4] demonstrated that mitosis is common in the muscle cells composing tumors of that type and occurs in fully differentiated cells with distinct myofibrils. As the stigma of tumor cells remains attached to the cells of myoma and as they cannot be considered as absolutely normal muscle cells, it is logical to extend the search for mitosis of muscle cells to uteri with hypertrophy of the myometrium, with use of the histologic methods suitable for the preservation of the finer details of the muscle cells and the mitotic figures.[4] That such proliferation of the muscle cells in myometrial hypertrophy occurs is shown in the case which I shall now describe.

REPORT OF A CASE

A Negro woman, 41 years old, gave the following history: One day before the expected date of menstruation (April 21, 1944) the flow had started and had been much stronger than usual. The menstruation had always been regular and normal. She had had two normal deliveries, the last one sixteen years before; after the birth of the second child, but many years ago, she had had a miscarriage. Appendectomy had been performed one year previously. On the clinical diagnosis of myoma uteri supravaginal hysterectomy was performed on May 5, 1944 (Dr. F. R. van de Stadt). The ovaries and tubes showed nothing abnormal. The postoperative course was uneventful. The uterus was enlarged; the anterior wall contained an almost completely necrotic myoma, about 6 cm. in diameter. The myometrium was thickened and pale, rose-white; the consistence was diminished. The endometrium was thin and showed nothing abnormal.

Microscopic Examination.—(*a*) Myoma: The myoma was almost completely necrotic; it contained much connective tissue. Only in the peripheral parts could a few viable muscle cells be found; they were much thinner than the muscle cells of the myometrium.



A muscle cell during mitosis. The centrally located myofibrils can be easily distinguished from the paler peripheral protoplasm. Masson's tetrachrome; × 600.

(*b*) Endometrium: The endometrium was relatively thin, and the cells of its stroma were loosely arranged. The glandular epithelium showed no signs of secretion. There were a few lymphocytes in the stroma. The veins were wide. The endometrium was evidently in the proliferative phase, as mitotic divisions occurred in

1. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 4, Philadelphia, W. B. Saunders Company, 1942, p. 161.
2. Stieve, H., cited by Meyer.[3]
3. Meyer, R.: Uterus und Tuben, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 7, pt. 2, p. 632.
4. Hartz, P. H., and Hugenholtz, M. J.: Am. J. Clin. Path. **12**:523, 1942.

the cells of the stroma, in the surface epithelium and in the epithelium of the glands. There was slight endometriosis interna.

(*c*) Myometrium: The myometrium was composed of the usual bundles of unstriated muscle cells, separated by loose connective tissue carrying the blood vessels and containing a few fibrocytes and histiocytes and an occasional lymphocyte or leukocyte. The muscle cells were large and broad and resembled the muscle cells of the pregnant uterus. All of them contained many distinct myofibrils, which were beautifully brought out by the Masson stain. Mitotic division occurred throughout the preparations, although its frequency varied from one place to another. Sometimes two or three mitotic figures could be counted in one field of a 2 mm. objective; in other places they were less frequent, especially in the stratum submucosum. The cells in mitosis showed all the characteristics of the mitotic muscle cells which we have already described,[4] especially the rounded swelling in the nuclear area and the interruption of the myofibrils by the perinuclear protoplasm. Another peculiarity, which was especially visible in the broad cells, was the tendency of the fibrils to group themselves centrally in the cell during mitosis, thus leaving the peripheral protoplasm free. I have also observed this phenomenon in mitosis of muscle cells in the media of small arteries and in myomas; according to my experience it is typical for the unstriated muscle cell. The myofibrils could be demonstrated in all dividing cells. The other special structures which belong to, or are particularly visible during, mitosis, such as achromatic spindles, centrosomes and, in the telophase, Flemming's intermediate body, were distinct. The chromosomes were perhaps a little larger than in the mitotic muscle cell in myoma. In the connective tissue no signs of proliferative activity could be observed, apart from an isolated mitotic figure in the endothelium of a small artery.

COMMENT

As follows from the foregoing description, mitotic figures occurred in a myometrium which on gross examination appeared hypertrophic. That pregnancy was not the cause of the proliferation of the muscle cells was proved by the gross and the microscopic examination of the endometrium. Likewise, good care was taken not to confound myometrium with myoma, and the possibility that the observation in reality concerned a very small, grossly invisible myoma with cells in mitosis is excluded by the fact that the mitotic figures occurred in a large area of the myometrium. That the myoma was the cause of the myometrial hypertrophy is not probable, as such hypertrophy is not common in the large myoma material of the Public Health Service laboratory in Curaçao, especially not in women of this age. The necrosis of the myoma and the hypertrophy are perhaps caused by the same factor, as happens in pregnancy. Hypertrophy of the myometrium such as that observed in this case is a regular finding in the clinical syndrome often named fibrosis uteri or metrorrhagia myopathica, which has recently been described by Williams and Kinney[5] as myometrial hypertrophy. In 10 cases in which specimens were examined microscopically these authors did not find muscle cells in mitosis, and they expressed the belief that the increase in size of the uterus is due to increased size of the muscle fibers of the myometrium and that the condition may represent an estrogenic effect. From a theoretic point of view it is important that the dividing muscle cells in this case showed many distinct myofibrils and did not differ in any respect from the rest of the muscle cells. They cannot, therefore, be classified as immature cells and thus there was marked proliferation of completely developed muscle cells without the presence of so-called myoblasts and partially developed muscle cells or intermediate forms between connective tissue cells and muscle cells. It must also be considered probable that proliferation of muscle cells plays a more important role in other forms of hypertrophy of the myometrium than is generally assumed.

SUMMARY

In the uterus of a 41 year old woman myometrial hypertrophy and a necrotic myoma were found. Microscopically, the myometrium showed numerous fully developed muscle cells, containing distinct myofibrils, in mitosis. Some characteristics of the mitosis of muscle cells are described.

5. Williams, J. T., and Kinney, T. D.: Am. J. Obst. & Gynec. **47**:380, 1944.

PERIARTERITIS NODOSA-LIKE LESIONS IN RATS FED THIOURACIL

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The occurrence of periarteritis nodosa–like lesions in animals has been reported by many observers—in a herd of axis deer by Lüpke [1] and Jaeger [2]; in cattle by Nieberle,[3] Trawinski,[4] Knösel [5] and Guldner [6]; in swine by Joest and Harzer [7] and Nieberle [8]; in dogs by Balô,[9] and in rats by Wilens and Sproul.[10] The last-named observers found typical periarteritic lesions in 9.7 per cent of 487 rats dead of natural causes. All the involved rats were old ones—the females averaging 856 and the males 700 days of age; 30, or 63.8 per cent, were females.

Following the original account of the disease in man by Kussmaul and Maier,[11] there was a general tendency to consider syphilis as a cause. Then for a period it was considered as a specific infection, probably a virus infection, and Haun [12] and Harris and Friedrichs [13] reported the production of lesions resembling periarteritis nodosa in guinea pigs and rabbits, respectively, by inoculating them with blood or with saline extracts of organs from persons who had the disease. These observations have not been confirmed.

Following the studies of Grüber,[14] who came to the conclusion that the disease was a manifestation of hypersensitivity, all later observers have accepted his general conclusion that the vascular reaction is not a response to a single excitant but rather the expression of hypersensitivity in the vessel wall where a preceding infection or intoxication has rendered the wall locally hypersensitive. This view is also supported by the finding of vascular lesions similar to periarteritis nodosa in fatal cases of serum sickness.

Recently Rich [15] and Rich and Gregory [16] have reviewed the subject and brought further evidence, both from the spontaneous occurrence of the disease in human beings and from the experimental production of similar lesions in rabbits with injections of foreign serums, that the disease is always an allergic reaction. Rich has also emphasized the possible association of hypersensitivity to the sulfonamide drugs with the disease. He reported a case of periarteritis nodosa following the use of sulfathiazole alone. The patient received the drug for five days when it was discontinued, and a second course of treatment was started with the same drug after an interval of seven days. Following this, the patient's condition grew worse rapidly, and he died on the nineteenth day after the first dose of sulfathiazole. This patient also had widespread focal inflammatory necrotic lesions in the viscera of the type described by Lederer and Rosenblatt.[17]

OBSERVATIONS ON LESIONS IN RATS FED THIOURACIL

Our special interest in this subject was the incidental finding of typical periarteritis nodosa–like lesions in 3 white rats, during the course of experiments on the effects of prolonged feeding with thiouracil (synthesized from thiourea). The principal data follow:

RAT 10o.—A young male adult, born in the laboratory and never used for other experiments, was fed 8 Gm.

From the Laboratory Division, Montefiore Hospital.
Thiouracil was generously supplied by Lederle Laboratories.

1. Lüpke, F.: Verhandl. d. deutsch. path. Gesellsch. **10**:149, 1906.
2. Jaeger, A.: Virchows Arch. f. path. Anat. **197**: 71, 1909.
3. Nieberle, K.: Virchows Arch. f. path. Anat. **269**:587, 1928.
4. Trawinski, A.: Arch. f. wissensch. u. prakt. Tierh. **59**:207, 1929.
5. Knösel, W.: Ztschr. f. Fleisch- u. Milchhyg. **41**: 413, 1931.
6. Guldner, E.: Virchows Arch. f. path. Anat. **219**: 366, 1915.
7. Joest, E., and Harzer, J.: Beitr. z. path. Anat. u. z. allg. Path. **69**:85, 1921.
8. Nieberle, K.: Arch. f. wissensch. u. prakt. Tierh. **76**:47, 1940.
9. Balô, J.: Virchows Arch. f. path. Anat. **248**: 337, 1924.
10. Wilens, S. L., and Sproul, E. E.: Am. J. Path. **14**:201, 1938.
11. Kussmaul, A., and Maier, R.: Deutsches Arch. f. klin. Med. **1**:484, 1866.
12. Haun, F.: Virchows Arch. f. path. Anat. **227**: 90, 1920.
13. Harris, W. H., and Friedrichs, A. V.: J. Exper. Med. **36**:219, 1922.
14. Grüber, G. B.: Virchows Arch. f. path. Anat. **258**:441, 1925.
15. Rich, A. R.: Bull. Johns Hopkins Hosp. **71**: 123 and 375, 1942.
16. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **72**:65, 1943.
17. Lederer, M., and Rosenblatt, P.: J. A. M. A. **118**:8, 1942.

daily of our regular diet containing 40 mg. (0.5 per cent) of thiouracil beginning on Nov. 16, 1943. This diet consists of hominy, rolled oats, meat scrap, dried milk, dried brewers' yeast and salt moistened with milk. In addition fresh greens—usually lettuce—were given daily. This rat was kept in a wire bottom cage with 5 other males. They were transferred to a clean sterilized wire bottom cage each week. This animal remained fairly active, ate well and had a clean coat until about Nov. 15, 1944, when rales were noted and its fur was erect. On December 6, the three hundred and eighty-sixth day of thiouracil feeding, a blood count showed 17,700 leukocytes and 5,200,000 erythrocytes. The rat was killed with chloroform and an autopsy made at once.

The body weight was 262 Gm. The thyroid gland weighed 0.172 Gm.; it was dark red and slightly granular. The thymus was involuted, and there were several enlarged lymph nodes in the area. The heart weighed 1.02 Gm. The middle lobe of the right lung was completely, and the lower lobe partially, consolidated. The upper lobe of the left lung showed patches of recent consolidation and was reddish, while the lower

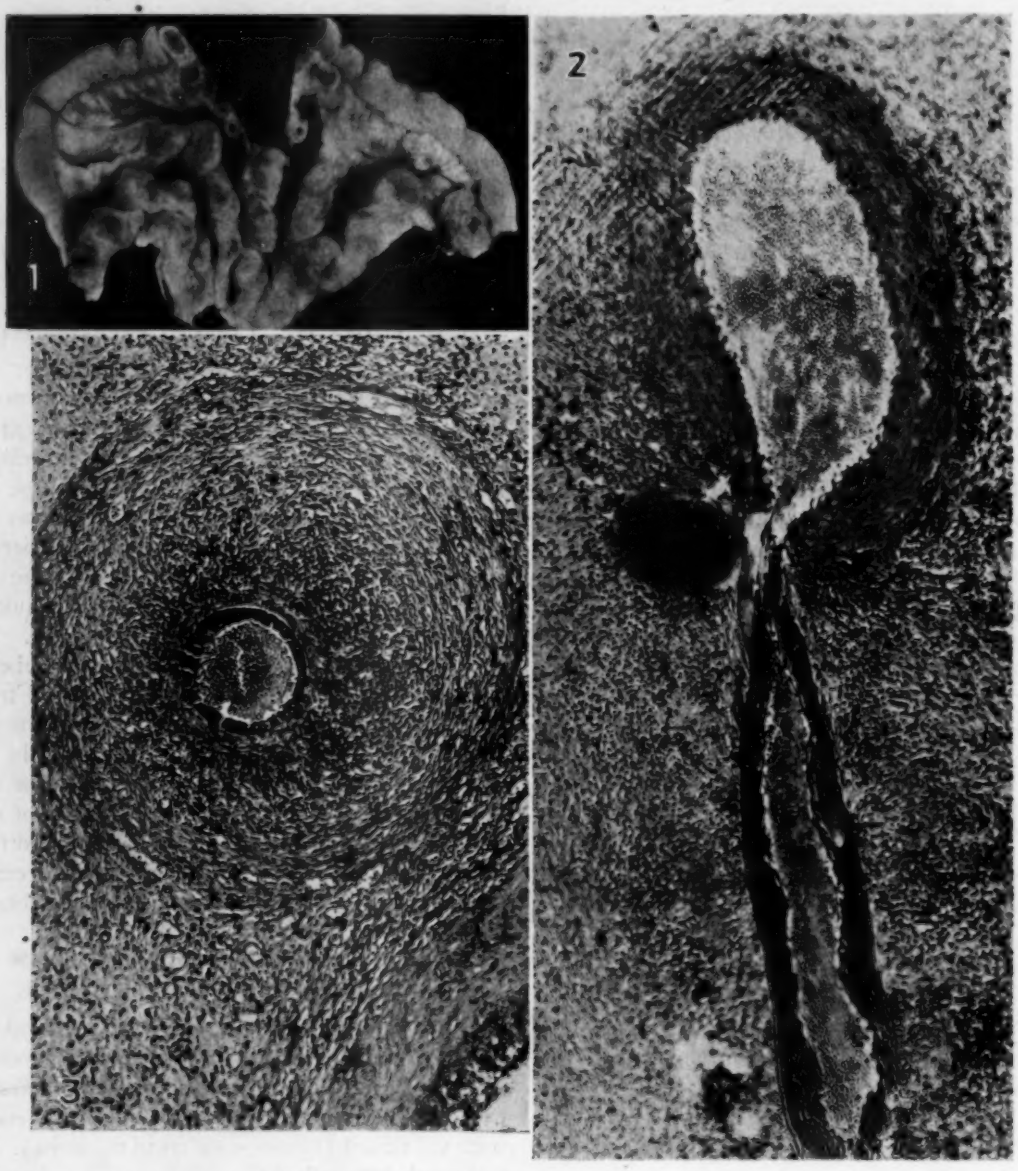


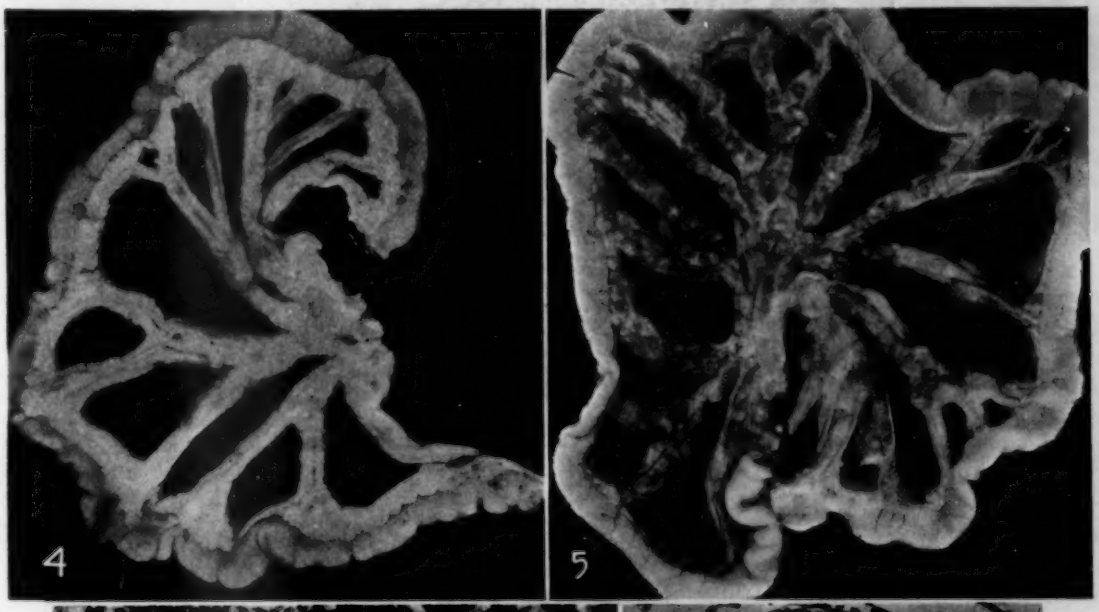
Fig. 1 (rat 10o).—A segment of the mesentery. Note the aneurysmal dilatations and the thick-walled, congested and thrombotic arteries.

Fig. 2 (rat 10o).—A medium-sized mesenteric artery with intact media and intima, showing a branch artery cut lengthwise. The latter shows fibrinoid necrosis of the subintima and the media, ending abruptly at its orifice. The endothelial lining is intact. There are moderate infiltration and fibrosis of the adventitia, more marked in the branch artery.

Fig. 3 (rat 10o).—A medium-sized artery in the pancreas showing advanced lesions with a complete ring of fibrinoid necrosis and extensive cellular infiltration and fibrosis of the media and the adventitia. Adjacent is a portion of the wall of a large artery without involvement.

lobe was completely consolidated and greenish gray, similar to the middle lobe. The spleen weighed 0.44 Gm. The liver was grayish purple. The pancreas was firm and edematous. The adrenal glands weighed 0.035 Gm. and were grayish brown. The kidneys weighed 2.02 Gm. Their cortices were slightly pitted. No calculi were found in the urinary tract. The testes weighed 0.78 Gm.; they were small but had normal outlines. The prostate and seminal vesicles together weighed 0.39 Gm. The hypophysis weighed 0.008 Gm. The mesentery (fig. 1) from the duodenum to the cecum was thickened and indurated, with no visible fat, and tortuous nodular cords fanned out from the base to the intestinal wall. These nodules were grayish brown and on section contained both fluid and clotted blood. The branches of the mesenteric vein appeared normal. There was slight enlargement of the mesenteric and peripancreatic lymph nodes, but the inguinal nodes were not enlarged. The aorta appeared normal.

Microscopic Examination.—The changes in organs which we considered definitely associated with thiouracil feeding were marked hyperplasia of the thyroid gland, involution of the adrenal cortex, hypertrophy of the adrenal medulla, shrinkage of the spleen, the testes, the prostate and the seminal vesicles and parenchymatous changes in the liver and the kidneys. The pneumonia was of the chronic snuffles type with a recent acute hemorrhagic bronchopneumonic spread. Enlargement of the mediastinal lymph nodes is always present in pneumonia. Enlargement and hyperemia of mesenteric lymph nodes, however, are usually not present in pneumonia and should, we believe, be considered as part of the periarteritis complex. The periarterial lesions were limited to the arteries of the mesentery, the pancreas and



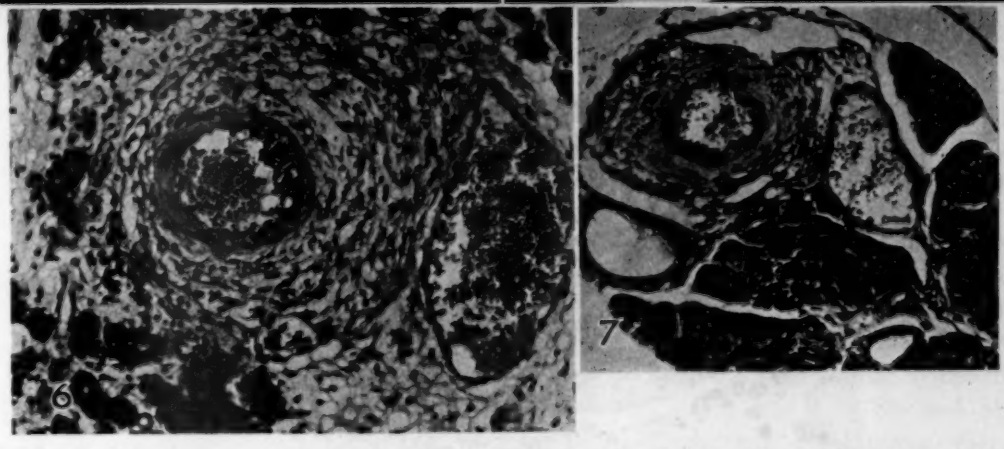


Fig. 4 (rat 15i).—A segment of the mesentery. There is only slight nodular thickening, masked by the normal fat.

Fig. 5 (rat 34a).—A segment of the mesentery. Note the thickened nodular arterial cords.

Fig. 6 (rat 15i).—A cross section of a small artery in the pancreas with very early fibrinoid necrosis visible at one point, with characteristic thickening and cellular infiltration of the adventitia. The accompanying vein is normal.

Fig. 7 (rat 15i).—A cross section of a small artery in the pancreas with very early perivascular infiltration. The accompanying vein is normal.

the retroperitoneal tissue at the base of the mesentery. The most advanced lesions were seen in the mesentery and the pancreas, where in any given section most of the arteries were involved, although one observed in any section a few relatively normal arterial walls. Figure 2 illustrates the local character of the lesion, which in this instance was limited to the branch artery at this level. The lesions were practically identical with those found in human periarteritis nodosa and need not be described in detail. In this rat there were arterial lesions in all stages—developing and healed. Outstanding was the extensive fibrinoid necrosis of the media and subintimal layers, often involving the entire circumference of the wall as a solid ring (fig. 3); in many instances, however, it appeared only as a focal area. The endothelial lining was usually intact even when the subintimal necrosis was extensive. However, it was over these areas of necrosis that one noted thrombus formation—sometimes fresh and at other times completely organized. The periarterial lesions were also present in all stages from acute edema and cellular infiltration to healing with extensive formation of granulation tissue. In this rat the edema, the cellular exudate and the formation of granulation tissue involved all of the mesentery and gave it the firm, thickened, semirigid condition noted in the gross examination. The walls of the branches of the mesenteric vein accompanying the arteries were not involved. The lymphatic vessels were irregularly dilated, somewhat thickened and contained many lymphocytes, attached to the endothelium. No arterial lesions were seen in sections of the lung, the liver, the spleen and the kidneys. In both kidneys

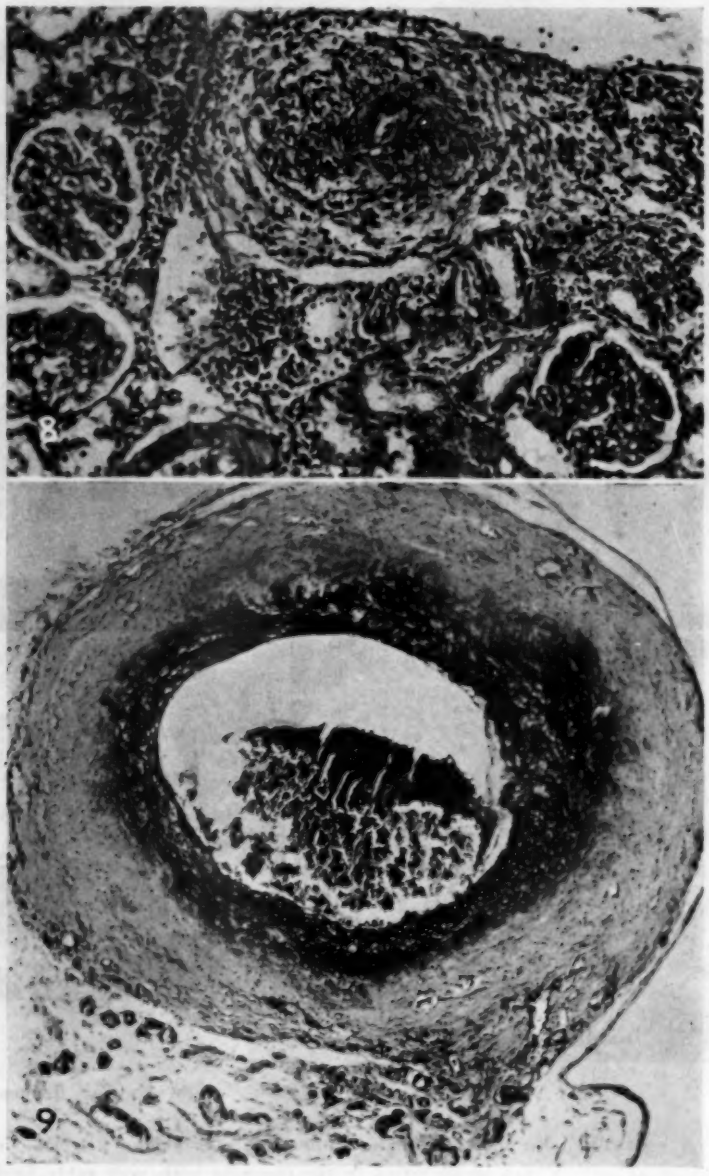


Fig. 8 (rat 15i).—A branch of a renal artery showing moderately advanced lesions. A small adjacent artery is not involved.

Fig. 9 (rat 34a).—Elastic tissue stain of a mesenteric artery. Note the healed lesion with prominent vasa vasorum.

there were calcific deposits in the collecting tubules and hyaline casts in localized areas.

RAT 15i.—A young female adult was fed our laboratory diet with 1 per cent (80 mg.) of thiouracil daily, beginning Feb. 1, 1944. This rat remained active until December 9, the three hundred and twelfth day of thiouracil feeding; then it seemed dull and was killed with chloroform on this day. The leukocyte count was 15,900.

The body weight was 152 Gm. The thyroid gland weighed 0.146 Gm. and was dark red. The thymus was atrophic, and there were several slightly enlarged lymph nodes in the area. Both lungs appeared normal throughout. The heart weighed 0.74 Gm. The spleen weighed 0.45 Gm. The liver was grayish purple. The pancreas was unusually white, moderately firm and edematous. The adrenal glands weighed 0.024 Gm. and were greenish gray. The kidneys weighed 1.39 Gm.; their surfaces were slightly pitted. No calculi were found in the urinary tract. The ovaries were small and contained several very small hyperemic corpora lutea. The pituitary gland weighed 0.009 Gm. The mesentery (fig. 4) showed slightly thickened and nodular cords radiating from the base to the intestinal wall, with the mesenteric veins appearing as sharply defined delicate red lines in a normal transparent mesenteric membrane containing fat. The intestinal wall was of normal size and appearance. The lymph nodes at the base of the mesentery and the peripancreatic and perigastric nodes were enlarged and hyperemic, but the inguinal and the axillary nodes were not enlarged.

Microscopic Examination.—Aside from the changes in the thyroid gland, the adrenal glands, the spleen and the ovaries and the parenchymatous change in the liver and the kidneys, which are considered as characteristic of thiouracil feeding, the special lesions were limited to the arteries of the pancreas, the mesentery, the kidneys and the peripancreatic and perigastric region. These lesions were essentially similar to, but of much less degree and more acute than, those described for rat 10o. There were no definite aneurysms, and thrombi were not seen (figs. 6, 7 and 8).

RAT 34a.—A female 7 months old was given our laboratory diet with 1 per cent (80 mg.) of thiouracil daily, beginning Jan. 29, 1945. Fifteen days later the rat became dull and dyspneic and was killed on the twenty-third day.

The body weight was 240 Gm. The thyroid gland weighed 0.183 Gm.; it was dark red and strikingly enlarged for so short a period of thiouracil feeding. The thymus was atrophic, and there were several enlarged nodes in the area. The upper and middle lobes of the right lung and the lower lobe of the left lung were completely consolidated. There were a few scattered areas of consolidation in the lower lobe of the right lung. The upper lobe of the left lung was emphysematous. The heart weighed 1.05 Gm. The spleen was large; the weight, 1.76 Gm. The pancreas was hyperemic, with nodular thickening of the arteries. The liver was grayish purple. The adrenal glands were enlarged, weighing 0.070 Gm. The ovaries contained large bright red corpora. The kidneys weighed 2.77 Gm. There were a few orange-colored calculi in the renal pelves. The pituitary gland weighed 0.0115 Gm. The mesentery of the small intestine (fig. 5) and of the descending colon showed nodular tortuous cords extending from the intestine to the base. Some of the nodules were yellowish but most of them were gray-brown. No vascular lesions were noted in the gastric vessels.

Microscopic Examination.—No acute lesions were seen in several blocks taken from the pancreas, the mesentery of the small intestine and the colon. The vessel walls were greatly thickened. This thickening was predominantly in the adventitial coat and consisted of a dense new formation of fibrous tissue, in which the vasa vasorum were strikingly enlarged, often congested and possibly increased in number (fig. 9). Scattered throughout this thickened adventitia but more frequently in the immediately adjacent areolar tissue were larger and smaller collections of macrophages filled with brownish pigment. Also in the areolar tissue were a few plasma cells and lymphocytes but no granulocytes. Occasionally irregular areas of calcification were seen in the dense hyalinized adventitial coat, but in no vessel was medial or subintimal calcification noted. The media was not sharply outlined either on the intimal or on the adventitial side. No inner elastic layer could be made out, and while some filaments of elastic tissue were seen in the outer zone of the media, the sharp line of demarcation between media and adventitia was lost because of the extensive fibrous tissue replacement of the media.

COMMENT

Three rats (2 females and 1 male) showing typical lesions of periarteritis nodosa were detected in a group of more than 100 rats kept under the same laboratory conditions and given thiouracil. In 2 of the 3 rats this pathologic change presumably developed toward the end of the long period of thiouracil feeding, although in 1 (10o) there was abundant evidence of chronicity (healing and healed lesions). The third rat had received thiouracil for twenty-two days, and the lesions were largely healed. The lesions occurred chiefly in the branches of the superior and the inferior mesenteric arteries, and in rat 15i, also in branches of the renal arteries. The regional lymph nodes were enlarged and hyperemic. No arterial lesions were found in the spleen, the liver, the heart, the lungs, the thyroid gland, the gonads or the intestines.

This distribution of the lesions was in the path of absorption from the gastrointestinal tract and may be significant, particularly if sensitization is in some way dependent on antigenic substances spreading from the perivascular lymphatics as Klotz [18] has suggested. Rats 10o and 34a had extensive chronic and acute pneumonia, while rat 15i showed no pneumonic lesions or other signs of infection. These rats had not been used for any previous experimental procedures, and we have no clue as to why this manifestation of hypersensitivity developed in only 3 rats. The question of whether thiouracil could be a factor is raised. Such an association does not seem likely since rat 34a had received the drug for twenty-two days and only the healed arterial deformities (hyalinization of the media, fibrosis and calcifi-

18. Klotz, O.: J. M. Research **37**:1, 1917.

cation in the adventitia) were present. However, one does not know how rapidly healing of the lesions can occur. If the disease in rats is similar to human periarteritis nodosa, the lesions may develop in a few days (Rich). The very high percentage (9.7) reported by Wilens and Sproul showed a more extensive distribution of lesions than was found by us. They suggested that possibly dietary factors may have influenced the incidence since only in 1 of 75 rats receiving meat and vegetables did the lesions occur while 46 of 356 rats whose diet lacked one or the other of these ingredients had the lesions. The cases reported by Wilens and Sproul occurred in old rats—mostly over 700 days of age—while the oldest of our 3 rats was less than 500 days old.

The patient with periarteritis nodosa whose case was reported by Rich and referred to in the foregoing paragraph received sulfathiazole on two occasions, which might be looked on as providing the sensitizing and testing doses, while our rats received the thiouracil continuously. Many authors [19] have warned against using the same sulfonamide drug when it is necessary to repeat the course of treatment since the various "toxic" reactions occur in a higher percentage of such cases.

In view of the work of Schönholzer,[20] Wedum [21] and others it seems possible that hypersensitivity was induced by specific thiouracil–protein conjugates from proteins or their hydrolytic products in the intestine, which were absorbed by way of the lymphatics and thus reached the arterial walls. The normal rat is difficult to sensitize with any antigen, but if adrenalectomized,[22] it is fairly easily sensitized to horse serum.

If the periarteritis nodosa–like lesions observed are allergic reactions, it is possible that the hypertrophy of the adrenal medulla and the severe injury of the cortex which we have reported [23] following prolonged thiouracil feeding in rats may have rendered them susceptible to sensitization similar to that which can be induced following adrenalectomy. Lesions morphologically similar to those of periarteritis nodosa in man are of fairly common occurrence in white rats. If these lesions are manifestations of hypersensitivity, the high incidence is somewhat paradoxic.

SUMMARY

Periarteritis nodosa developed in 3 rats, 1 male and 2 females, reared in the laboratory, during continuous feeding with 0.5 per cent and 1 per cent thiouracil. About 100 other rats of the same stock and age fed with thiouracil did not show such lesions. The lesions were confined to the mesentery of the small intestine, the colon, the pancreas, the perigastric and peripancreatic region and the kidneys of 1 animal (15i). Two of the rats had extensive chronic and acute pneumonia; the third had no signs of infection. Neither rat had been previously used. All 3 rats showed approximately the same changes in the thyroid gland, the spleen, the gonads, the liver, the kidneys and the adrenal glands that are associated with thiouracil poisoning.

19. Dowling, H. F., and Lepper, M. H.: Am. J. M. Sc. **207**:349, 1944.

20. Schönholzer, G.: Klin. Wchnschr. **19**:790, 1940.

21. Wedum, A. G.: J. Infect. Dis. **70**:173, 1942.

22. Flashman, D. H.: J. Infect. Dis. **38**:461, 1926.

23. Marine, D., and Baumann, E. J.: Hypertrophy of the Adrenal Medulla of White Rats in Chronic Thiouracil Poisoning, Am. J. Physiol., to be published. Baumann, E. J., and Marine, D.: Involution of the Adrenal Cortex of Rats Fed with Thiouracil, Endocrinology, to be published.

Case Reports

LATENT PRIMARY CARCINOMA OF THE THYROID GLAND

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A mass in the neck is usually the initial finding in most cases of cancer of the thyroid gland. In a small percentage of cases the first symptoms may be caused by precocious metastases in remote viscera. As Willis [1] pointed out, in the large majority of instances latent cancer of the thyroid becomes manifest through deposits in the bones. In such cases the diagnosis of metastatic cancer of the thyroid gland is often made only after surgical operation on a limb and subsequent histologic examination of the osseous tumor have identified the thyroid origin. Willis also recorded from the literature hepatic, intestinal and cerebral metastases that were operated on and later proved to be secondary deposits from latent cancer of the thyroid gland. No instance in which pulmonary metastases from a primary tumor of the thyroid gland giving rise to the clinical picture in the case now reported has been found described in the available literature.

REPORT OF A CASE

The patient was a 51 year old white woman who first became ill in the summer of 1943. At that time she noted gradually increasing fatigability, anorexia and loss of weight. Several months later cough appeared with expectoration of whitish mucoid sputum which was occasionally blood streaked. Two months before admission to the Mount Morris Tuberculosis Hospital she noted marked dyspnea, which had become increasingly severe. A roentgenogram of the chest in June 1944 showed numerous nodular and linear densities scattered throughout both lung fields. She was admitted on July 7, 1944.

There were signs of scattered areas of pulmonary consolidation, moderate exophthalmos and moderate emaciation. No masses were felt in the neck. The white blood cell count was 14,200, with 84 per cent polymorphonuclear leukocytes, 4 per cent monocytes and 12 per cent lymphocytes. The red blood cell count was 5,000,000, with a hemoglobin content of 16.5 Gm. per hundred cubic centimeters (116 per cent). The sputum was negative for tubercle bacilli on three occasions. Roentgenograms of the chest revealed irregularly shaped and variably sized nodular and linear densities in the right lung, particularly below the level of the fourth anterior rib. In the left lung densities similar to those seen in the right lung were found between the levels of the first and third ribs anteriorly. Throughout both lungs there were irregularly outlined areas of radiolucency which were suggestive of small areas of cavitation. Comparison of this roentgenogram with that of June 1944 showed definite increase in infiltration throughout both lungs. Despite vigorous supportive therapy, the patient failed rapidly and died after six days in the hospital.

Autopsy (one hour after death).—There was moderate emaciation. The thyroid gland was not palpable. No lymphadenopathy was apparent externally. The breasts were small and atrophic, and no masses were felt within the mammary parenchyma.

The left pleural cavity contained 500 cc. and the right pleural cavity 750 cc. of a clear straw-colored fluid. There were about 150 cc. of a similar fluid in the pericardial sac. No enlarged lymph nodes were seen in the mediastinum.

The heart was not enlarged. Several indurated, slightly elevated nodules 0.1 cm. in diameter were present beneath the visceral layer of the pericardium near the base of the heart. No tumor nodules were seen in the myocardium.

The left and right lungs, although not enlarged, weighed 840 and 960 Gm. There were no adhesions in either pleural cavity. Minute yellow-gray streaks were noted beneath the visceral pleura of both lungs. On section innumerable rounded and irregularly oval granular opaque gray-white nodules were seen scattered throughout both lungs from apex to base (fig. 1). The nodules were extremely firm. Many of them appeared to be formed by confluence of smaller foci. Where the pulmonary parenchyma was visible, tiny nodules measuring less than 0.1 cm. were noted. At the base of the right lower lobe was a roughly quadrangular focus of dark red tissue measuring 4 by 2 by 2 cm., slightly elevated above the level of the surrounding tumor-bearing pulmonary parenchyma. The major bronchi showed no areas of ulceration and contained no tumors. There were no thrombi in the larger branches of the pulmonary arteries.

On the anterior border and surface of the spleen were numerous thin-walled cystic structures measuring from 0.1 to 0.5 cm. in diameter. On section these appeared to be limited to the capsule. They contained a small amount of homogeneous yellow-brown material.

All lobes of the liver were occupied by numerous rounded and irregular foci of granular opaque gray-white tissue ranging in size from 0.3 to 4 cm. The nodules were well demarcated from the brown-red hepatic parenchyma. Occasionally, grayish streaks could be seen extending into the sinusoids. No gross invasion by tumor tissue was seen in either the portal or the hepatic venous channels.

The gallbladder wall was slightly thickened and contained about 50 calculi, faceted and dark green. The extrahepatic bile ducts were patent.

The kidneys contained several small nodules in the cortex, for the most part directly beneath the capsule.

The cervix uteri was indurated, and a small red polyp protruded into the endocervical canal. The endometrium was smooth and glistening throughout. A small myomatous nodule was present in the myometrium. A few tiny cystic structures were noted beneath the serosa covering the posterior surface of the uterus. In

From the Mount Morris Tuberculosis Hospital, Tuberculosis Division, New York State Department of Health.

1. Willis, R. A.: The Spread of Tumors in the Human Body, London, J. & A. Churchill, Ltd., 1934.

the right broad ligament was a thin-walled cystic mass measuring 3 cm. in diameter. It was attached to the region of the fallopian tube by a thin stalk.

The thyroid gland was not increased in size, but a firm mass was felt in the right lobe. The left lobe showed no abnormalities. On section of the right lobe a rounded mass measuring 1.25 cm. in diameter was noted in the anterolateral aspect of the lobe (fig. 2). The mass was opaque and gray-white, with prominent centrally placed hemorrhagic streaks and yellow areas of necrosis. The nodule was depressed below the level of the brown thyroid parenchyma. The capsule was

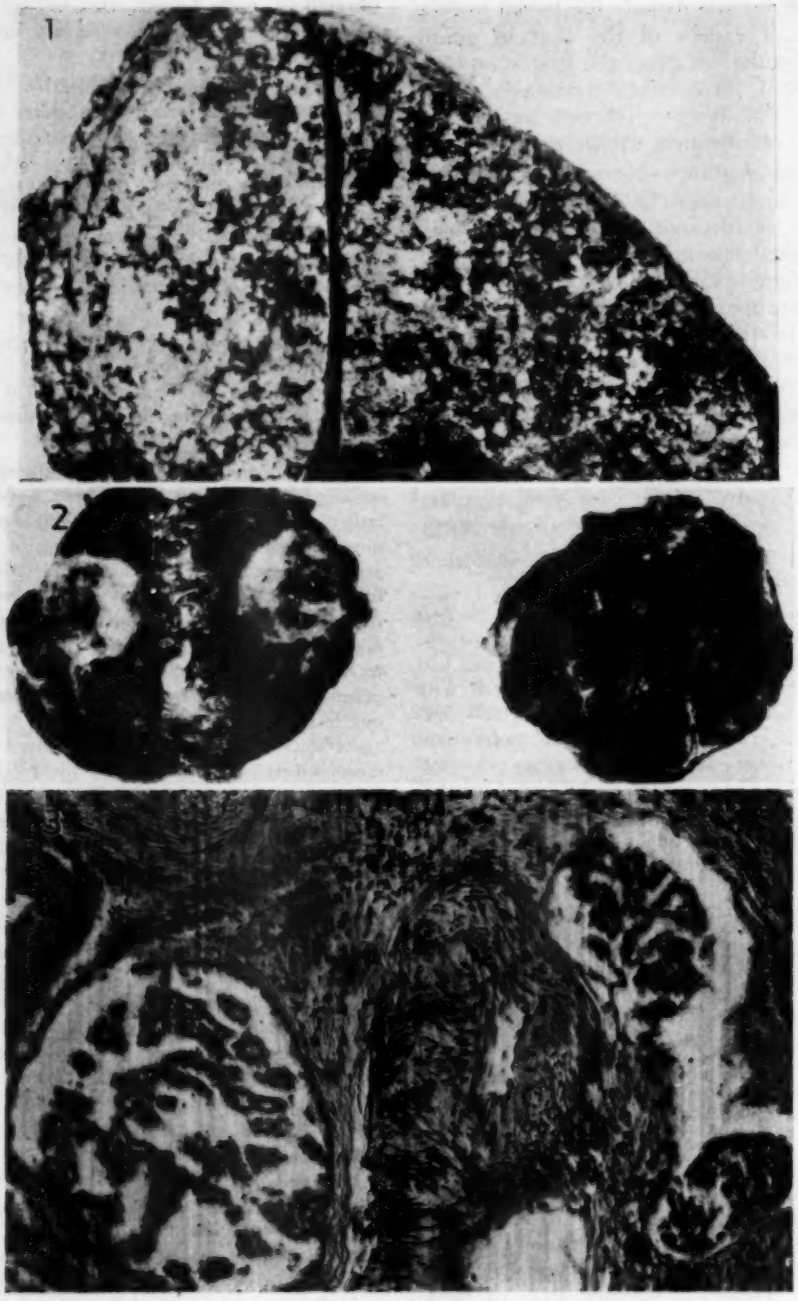


Fig. 1.—Cut surface of the left lung showing minute rounded and larger irregular confluent nodules of metastatic cancer; × 0.5.

Fig. 2.—Both lobes of the thyroid gland sectioned in the horizontal plane. The left lobe contains no tumor tissue. The cancerous mass in the anterolateral aspect of the right lobe has invaded a small portion of the capsule of the gland. In the center of the mass hemorrhage and necrosis are prominent; × 1.4.

Fig. 3.—A section through the myometrium showing the uterine venules filled with solid plugs of cancerous tissue in which papillation is prominent. Section of paraffin-embedded tissue stained with hematoxylin and eosin; × 120.

invaded by the tumor tissue in one small area. No obvious involvement of regional lymph nodes and no vascular invasion were seen on gross examination.

A sagittal section through the lumbar vertebrae revealed extensive replacement of the hemopoietic tissue by opaque gray-white almost bony hard tissue.

Microscopic Observations.—The most prominent histologic change in many of the viscera was extensive intravascular proliferation of tumor cells. In the heart, groups of epithelial cells were noted in an occasional myocardial venule. The epicardial venules and the vasa vasorum of the aorta were filled with solid plugs of tumor tissue in papillary formation. The interlobar and interlobular veins of the pancreas contained cancer cells with an alveolar pattern. In the liver many parenchymal metastases were present. The tumor tissue extended into the walls and lumens of the portal and hepatic venous radicles. Tiny nodules of metastatic cancer were present in the adrenal cortex; the capsular venules contained small tumor emboli. Although several metastatic nodules were observed in the renal cortex, no definite tumor cells were seen within the renal vessels. The pelvic viscera showed the most widespread and extensive permeation of veins by the cancerous tissue. In the uterus particularly, almost every venule and many of the lymphatic channels contained solid masses of cancerous epithelial cells (fig. 3). The ovarian venules were similarly involved by papillary tumor tissue.

The small trabecular veins of the spleen contained occasional epithelial cells similar to those in other vessels. No true metastatic foci were found in the splenic parenchyma. A multilocular lymphangioma was present in the capsule of the spleen and corresponded to the cystic structures noted grossly. The cysts were lined by either flattened endothelium-like cells or low cuboidal cells. The lumens of the cystic spaces were occupied by very pale eosinophilic homogeneous material containing a few histiocytic cells. Adjacent to and within some of the cysts were small nodules of papillary neoplastic tissue identical with many of the foci noted in other organs.

Isolated groups of carcinomatous cells were found in the venous sinusoids of the vertebral marrow. Prominent new bone formation was seen alternating with cancer cells within the marrow. Rows of osteoblastic cells were present at the periphery of many of the new spicules of bone, and it was difficult to dissociate them from the cancerous epithelium. Many of the solid neoplastic foci showed prominent papillary formation. No actual destruction of the bony trabeculae of the marrow was seen.

Little intact parenchyma remained in the lungs. Many sections showed the bulk of the pulmonary tissue to be occupied by papillary epithelial tumor tissue. Tiny discrete and larger confluent foci were scattered throughout. In the smaller nodules the tumor occupied the lumens of the alveoli, and the interalveolar septums were intact. In the larger confluent foci the interalveolar walls were poorly delineated because of compression by the tumor cells. In some situations necrotic and necrobiotic changes were noted. Densely basophilic oval bodies composed of finely laminated amorphous material and resembling the so-called corpora amylacea were observed both in the necrotic foci and in places where the cells were intact (fig. 4). Calcium could be demonstrated in a few of these structures by the von Kossa stain. Extensive permeation of the blood vessels and the lymphatic channels by the cancerous tissue was evident. The pulmonary veins were predominantly involved. The lumens of these vessels were filled with solid clumps of cancer cells. Some of the larger pulmonary arteries contained recently formed thrombi in which could be seen large collections of cancer cells, some of which were arranged in glandular formation. Some of the bronchial arterial branches were filled with small plugs of tumor tissue. The perivascular and peribronchial lymphatic vessels, as well as the subpleural lymphatic channels, were filled with small tumor thrombi.

The left lobe of the thyroid gland contained no tumor tissue. In the right lobe the rounded nodule seen grossly, which was obviously carcinomatous, was flanked by a small papillary adenocystoma on one side (fig. 5) and a colloid adenomatous nodule on the other.

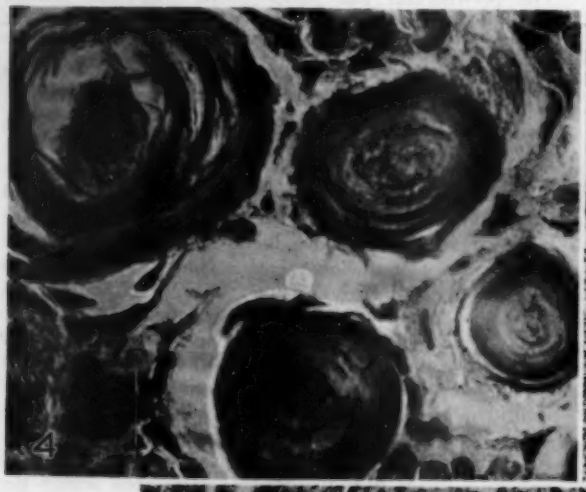
In contrast with the normal neighboring thyroid parenchyma, the alveoli in the cancerous nodule were placed more closely, and there was almost complete disappearance of the interacinous connective tissue. In addition the cells comprising the alveoli within the cancerous nodule were larger, distinctly hyperchromatic and variable in size and shape (fig 6). In some acini there was a moderate amount of colloid, while in others the colloid was scanty or absent. Active growth could be identified in some of the thyroid follicles by the presence of small papillations composed of epithelial cells. In other alveoli this tendency was more pronounced and solid plugs of epithelial cells were seen within the lumens. In places the cancer cells were growing in cords and clumps without any attempt at gland formation. Clumps of cancerous cells which were markedly hyperchromatic extended beyond the limits of the roughly rounded cancer nodule. The capsule of the thyroid gland was invaded at one point, and clumps of cancer cells were seen to extend between the normal thyroid acini of the regional lobules. Prominent venular invasion by small groups of epithelial cells was noted. Solid clumps of epithelial cells were present in the lumens of these vessels, and occasionally the endothelium had been replaced by a single row of neoplastic elements. Extensive hemorrhage and necrosis were present in the center of the cancerous nodule. A large amount of fibrous tissue was also centrally located and was composed of broad bands of afibrillar, densely eosinophilic homogeneous collagen in which there was only an occasional fibroblastic cell. In some places the collagenous tissue was entirely acellular.

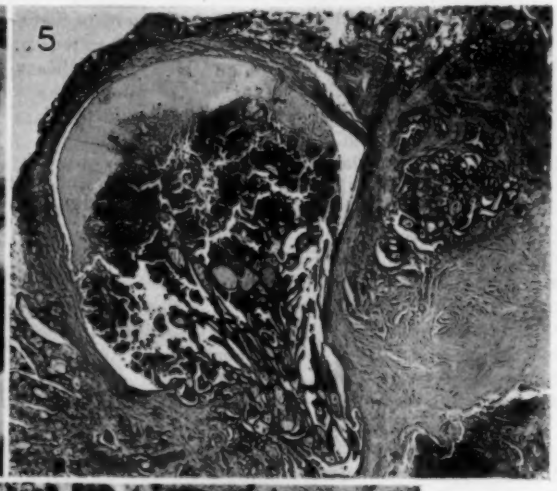
The papillary adenocystoma, which measured approximately 0.3 cm. in diameter, was rimmed peripherally by a thin layer of fibrous connective tissue on which rested a single layer of cuboidal epithelium. In the center the papillary projections were seen in cross section and appeared as rounded alveolar structures with a central core of slightly vascularized connective tissue. The epithelial cells were regular in size and shape, and no atypical proliferation was visible. A moderate amount of colloid was seen in the alveoli and in the lumen of the cyst between the papillary projections and the cyst wall. The colloid adenomatous nodule approximated the dimensions of the adenocystoma described and was composed of various-sized acini with abundant colloid in the center of the glands. The epithelial linings were made up of flattened cuboidal cells.

Anatomic Diagnosis: Papillary adenocarcinoma of the right lobe of the thyroid gland with metastases to the lungs, visceral pleura, visceral pericardium, liver, kidneys, lumbar vertebrae, splenic capsule and adrenal glands; neoplastic embolism of myocardial, splenic, pancreatic, ovarian and myometrial venules; hydrothorax; hydropericardium; recent hemorrhagic infarct of the lower lobe of the right lung; multilocular lymphan-

gioma of the splenic capsule; fibrolipoma of the kidney; hydatid of Morgagni of the right broad ligament; serosal cysts of the uterus; small leiomyoma of the uterus; adenomatous polyp of the cervix; chronic cholecystitis and cholelithiasis; old tubercles of the spleen.

It was stressed that the term "latent" should be applied to any cancer the presence of which was made known by metastatic deposits in remote viscera before any symptoms or signs referable to the site of the cancer's origin had appeared. The cancer now described seems to fit





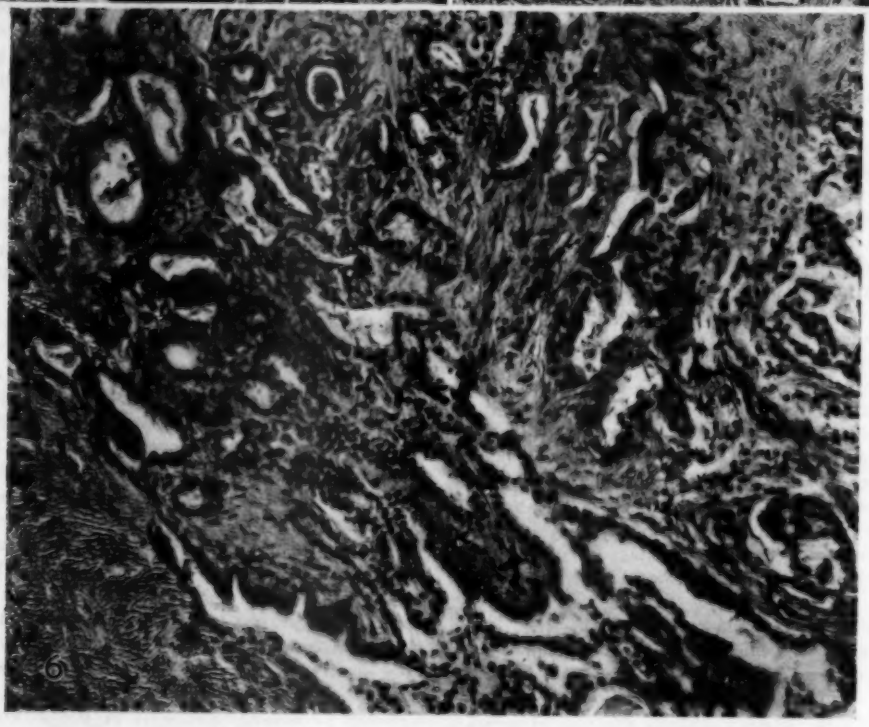


Fig. 4.—Densely basophilic oval bodies composed of finely laminated amorphous material found in a portion of one of the pulmonary metastases in which necrosis was not prominent. Shadow forms of epithelial nuclei are present in the centers of some of the bodies. Section of paraffin-embedded tissue stained with hematoxylin and eosin; × 590.

Fig. 5.—A hyperplastic papillary adenocystoma is situated between the cancerous mass at the right and the normal thyroid acini at the left. Necrosis and hyaline fibrosis may be noted within the cancerous nodule. Section of paraffin-embedded tissue stained with hematoxylin and eosin; × 14.

Fig. 6.—The cells comprising the thyroid acini within the cancer nodule are hyperchromatic, and atypical proliferation is seen.

COMMENT

A precise definition of latent primary carcinoma following that proposed by Willis has been offered by Gewanter, Mitchell and Angrist.[2]

2. Gewanter, A. P.; Mitchell, N., and Angrist, A.: Arch. Path. **35**:66, 1943.

into that category. The thyroid mass was neither palpable nor visible, nor did it occasion any symptoms. Suggestive exophthalmos was noted when the patient was admitted to the hospital, but the probability exists that this isolated sign was caused by the physiologic activity of the widespread metastases. In this connection it is interesting to speculate about the significance of the densely basophilic oval bodies which were found in some of the metastatic nodules, for such concretions, which were found intimately associated with degenerative and necrotic changes in the cancerous epithelium, may represent some form of altered thyroid secretion. Exophthalmos had not been noted before admission, and there were no other symptoms of overactivity of the thyroid gland.

Inaccessibility and prominent vascular invasion both contributed in making this tumor a latent one. Despite the superficial location of the cancer in the right lobe of the thyroid gland, its small size and its failure to elevate the capsule in any one place precluded clinical discovery of the mass. The ribbon muscles of the neck effectively hid the small tumor from the examining fingers. Equal importance must be attributed to the early and extensive growth of the cancer cells within the venules of the thyroid gland. The initial symptoms were referable to the lungs, and this attests well to the fact that the pulmonary metastases were established early in the course of the disease and grew rapidly while the primary growth was relatively quiescent. The tendency of these particular cancer cells to penetrate vascular channels is well shown in the metastatic foci in the lungs and the liver. The pulmonary veins were extensively involved by tumor thrombi, and this afforded adequate opportunity for further dissemination of the tumor to viscera in the path of the systemic circulation. In turn, the invasion of the large hepatic veins by metastatic nodules in the liver was another prolific source of pulmonary metastases. The permeation of the branches of the bronchial arteries by microscopic tumor emboli provided yet another mechanism of pulmonary seeding.

The prominent involvement of the lungs and the tendency of the pulmonary metastases to line the alveolar walls simulate the appearance described for primary alveolar cancer of the lung. From the observations in this and other cases of small latent primary carcinoma of the thyroid and the prostate gland, the diagnosis of primary alveolar cancer of the lung should be made only after careful search for all such possible distant foci of origin.

The genesis of the diffusely scattered venous permeation in various organs is open to question. That the cancerous intravascular growths do not represent tertiary venous invasion is suggested by the absence of discrete metastatic nodules in the organs affected. It is difficult to visualize such widespread involvement of the ovarian and myometrial venules from simple postmortem manipulation of the viscera. Retrograde venous embolism must be considered despite the absence of gross occlusion of the larger veins (which is stressed by Willis), because of the widespread obstruction of the venous channels in the pulmonary and portal beds. Finally consideration must be given to permeation by extensive contiguous growth within the venous channels from undisclosed arterial emboli.

It has been said that in 80 to 90 per cent of all cases of carcinoma of the thyroid gland the carcinoma arises from preexisting adenoma [3] and that "usually the development of the adenocarcinoma has destroyed all trace of the pre-existing adenoma and this original nidus can be recognized only from the history given by the patient." Despite the absence of such a history in this case, there is histologic evidence of preexisting adenoma. Adjacent to the cancerous nodule there were a well developed benign papillary adenocystoma and a colloid adenomatous nodule. The wide bands of deeply eosinophilic homogeneous acellular fibrous tissue in the large cancerous nodule also indicate that another lesion of many years' duration must have been present.

Histologically, this cancer of the thyroid fits into group 2 of the classification proposed by Lahey, Hare and Warren [3] and others.[4] While there was considerable anaplasia in the primary tumor as well as in some of the metastases, the bulk of the tumor showed prominent papillary formation.

SUMMARY

In the case of latent primary carcinoma of the thyroid gland presented, there is evidence that the cancer arose at the site of an adenoma of long standing. The presenting clinical picture was one of pulmonary involvement and was caused by early and prolific metastases in the lungs.

The small size of the primary tumor, without distortion of the gland, the invasion of the venules of the gland by the cancer cells and the rapid growth of the metastatic foci in the lungs account for the latency in this case.

A prominent feature of the tumor was its widespread permeation of veins throughout all the areas of involvement.

The gross and microscopic pulmonary changes bore a resemblance to primary alveolar cancer of the lung.

3. Lahey, F. H.; Hare, H. F., and Warren, S.: Ann. Surg. **112**:977, 1940.

4. McClintock, J. C.; Klinck, G. H., Jr., and Conrad, J. E.: Surg., Gynec. & Obst. **72**:150, 1941.

ADRENAL CORTICAL ADENOMA OF THE EPIDIDYMIS

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Nodules of tissue repeating the structure of cortical adenoma of the adrenal gland and displaced along the course of the wolffian duct or its adult derivative structures have been described frequently. In the publications reviewed by Nelson,[1] Glynn [2] and others these nodules are described as found near the adrenal gland, beneath the capsules of the kidney and the liver, along the course of the ovarian artery and vein, in the broad ligament of the ovary and in the ovary itself, along the course of the spermatic artery and vein and in the connective tissue of the inguinal canal. However, only a few nodules have been described which occurred in the region of the testis or the epididymis in man.

Dagonet [3] described 2 nodules of adrenal cortical tissue, 1 on the right spermatic vein and 1 between the right epididymis and the adjacent tubules of the corresponding testis in an infant aged 21 days. Micheal [4] recorded 7 cortical adenoma nodules occurring between the testicular tubules and the epididymal ducts; 4 occurred in adults and 3 in infants. Two heterotopic nodules were near the right epididymis in one infant, and 1 was near the left epididymis in another. Wiesel [5] reported the examination of 15 pairs of testicles and epididymides from newborn infants and an equal number from males whose ages ranged between 1 and 60 years. He found cortical adrenal gland tissues repeatedly near the testis and the epididymis in specimens from the newborn but only 2 adenomas among the tubules of the epididymis. Kirkbride [6] examined 54 tissues and reported 8 small adrenal cortical adenomas in the region of the testis and the epididymis. Berger,[7] R. Meyer,[8] Panã,[9] Pilliet, Regaud and Loisel, according to Glynn,[2] Roth, according to Ulrich,[10] Monserrat and Latienda,[11] and others observed similar nodules of adrenal cortical tissue in this region. Although the number of these heterotopic cortical adenomas reported in newborn and other male infants is small, the number observed in this region in adults is much less.

Jaffe [12] stated that accessory nodules disappear with advancing age because they are physiologically unnecessary in the presence of adequate normal adrenal glands. Others agree that most of these rests disappear before puberty. Wiesel [5] found cell masses and strands resembling cortical tissues near the epididymis in tissues from youths but none fully developed in the epididymis in tissues from adults. Micheal reported cortical tissues among the tubules of the right epididymis in 4 adults. Marsella,[13] in 1934, described a nodule among these ducts of the epididymis in a man aged 34 years, and Nelson [1] reported nodules in the region of the testis and the epididymis in 6 men. The tissues which Nelson examined were either within or just outside the tunica albuginea and either behind or just above or below the rete testis. His report discussed the individual characteristics in detail. All of these accounts of heterotopic tissue in newborn infants and in adults have the microscopic structure of the glomerular and fascicular zones of the adrenal gland.

REPORT OF A CASE

A white man aged 73 years entered St. Luke's Hospital, where routine examinations established a diagnosis of glioma of the temporal lobe of the right cerebral hemisphere. The postmortem examination, one month later, confirmed this diagnosis. No heterotopic adrenal gland tissues were observed grossly in the viscera, and these included the adult derivative structures of the wolffian ducts. Each adrenal gland weighed 10 Gm. and was not unusual. Histologic examination of the testes showed the usual characteristics. In the sections from one including the epididymis, the rete testis and the testicular tubules, a nodule of adrenal cortical tissue, 4 by 1 mm. in its external dimensions, was observed in the connective tissue outside the tunica albuginea posteriorly, at a level which corresponded to the level of the rete testis and between the tubules of the epididymis. This tissue was partially encapsulated. The cells (*A* and *B* in the figure) corresponded in structure and arrangement to the glomerular and fascicular zones

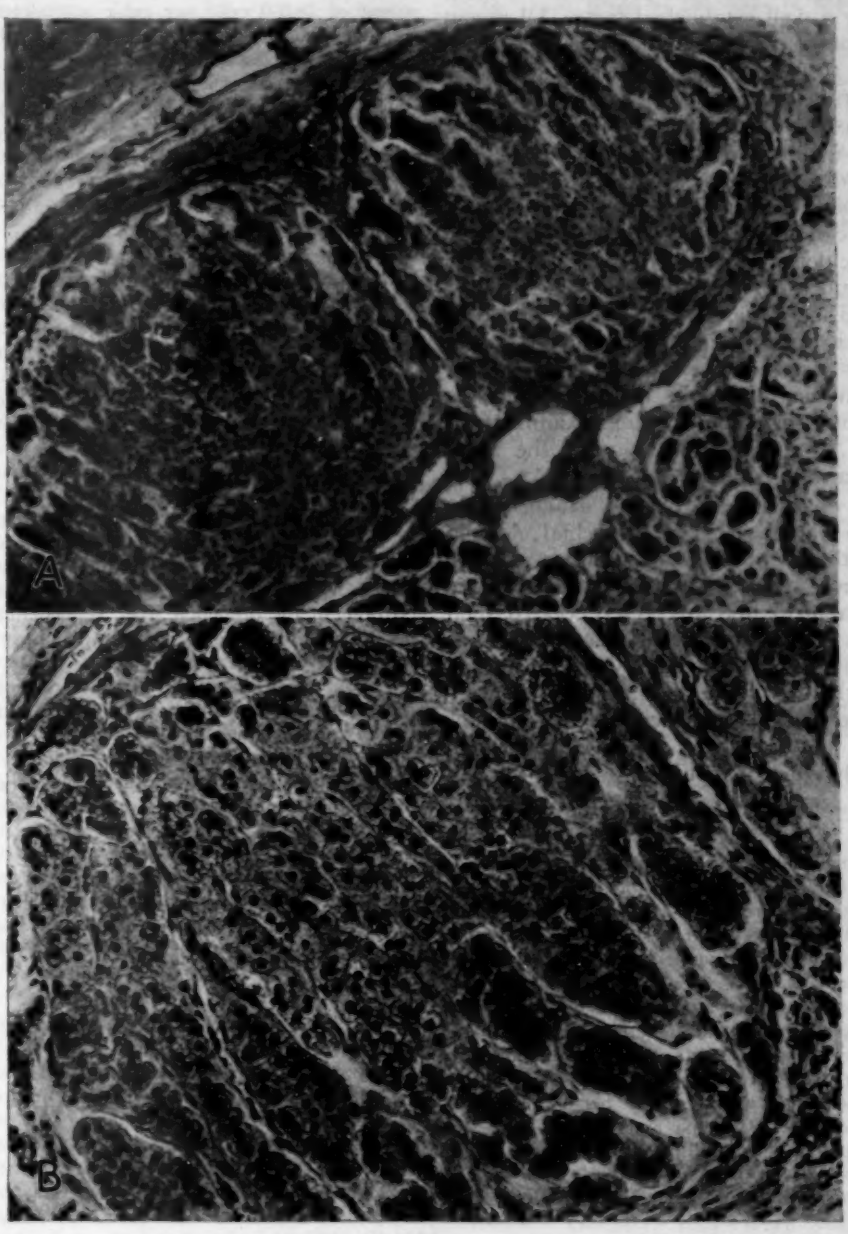
From the Henry Baird Favill Laboratory, St. Luke's Hospital.

This study was aided by the Winfield Pack Memorial Fund.

1. Nelson, A. A.: Arch. Path. **27**:955, 1939.
2. Glynn, E. E.: J. Obst. & Gynaec. Brit. Emp. **28**:23, 1921.
3. Dagonet, J.: Ztschr. f. Heilk. **6**:1, 1885.
4. Micheal, J.: Deutsches Arch. f. klin. Med. **43**: 120, 1888.
5. Wiesel, J.: Wien. klin. Wchnschr. **11**:443, 1898.
6. Kirkbride, M. B.: Arch. f. Entwcklngsmechn. d. Organ. **32**:717, 1911.
7. Berger, L.: Arch. d'anat. micr. **32**:315, 1936.
8. Meyer, R.: Ztschr. f. Geburtsh. u. Gynäk. **71**: 221, 1912.
9. Panã, C.: Minerva med. **1**:76, 1931.
10. Ulrich, A.: Beitr. z. path. Anat. u. z. allg. Path. **18**:589, 1895.
11. Monserrat, J. L., and Latienda, R. I.: Arch. Soc. argent. de anat. norm. y pat. **5**:367, 1943.
12. Jaffe, H. L.: Arch. Path. **3**:414, 1927.
13. Marsella, A.: Arch. ital. di urol. **11**:281, 1934.

of the adrenal gland. The cords of cells opposite to those partially encapsulated were in rows separated from each other by strands of fibrous connective tissue. This histologic structure was identical with that characterizing the cells of cortical tissue. Cells of the reticular zone, as well as aggregates of medullary tissues of the adrenal gland, were absent.

curred in the region of the testis and the epididymis. The information available is not sufficient to establish the incidence of these nodules in newborn infants, older infants or adults. They seem to be less frequent in adults. Perhaps accessory nodules atrophy with age in the pres-



A, photomicrograph (low power) illustrating the nodule of heterotopic adrenal gland tissue in the epididymis. Two small ducts are at the upper edge. *B*, photomicrograph illustrating the zonal arrangement and vacuolated cytoplasm of the cells (× 198).

SUMMARY

Nodules of tissue repeating the structure of cortical adenoma of the adrenal gland and displaced along the course of the wolffian duct or its adult derivative structures have been described frequently. Of these, only a few nodules occurred in the region of the testis and the epididymis. The information available is not sufficient to establish the incidence of these nodules in newborn infants, older infants or adults. They seem to be less frequent in adults. Perhaps accessory nodules atrophy with age in the presence of the usual adrenal gland tissues, but many of them probably are not observed or recorded. This report adds another to the few records of adrenal cortical adenoma heterotopic between the tubules of the epididymis and the rete testis in an aged man.

BRONCHIAL ASTHMA AND TUBERCULOSIS

PETER A. HERBUT, M.D., PHILADELPHIA

That bronchial asthma and pulmonary tuberculosis can occur in the same patient at the same time is today a well established fact. All recent and some not so recent publications deal with the subject from a purely clinical approach. Some authors studied the incidence of tuberculosis in asthmatic patients,[1] whereas some reported the incidence of asthma in tuberculous patients,[2] and others still made no statistical studies but simply described the two diseases as occurring concomitantly in the same patients.[3] Since the incidence of asthma in patients with pulmonary tuberculosis is given as only 0.25 per cent to 3.1 per cent [2] and the incidence of tuberculosis in asthmatic patients as 4.4 per cent,[1d] 6 per cent,[1b] 8 per cent [1c] and 10 per cent,[1a] the number of deaths must be relatively few and the number of postmortem examinations fewer still. At any rate, in none of the more recent publications is there any mention of histopathologic observations of the tracheobronchial tree in fatal cases of bronchial asthma associated with tuberculosis, and neither in these reports nor in a search of the medical literature have I been able to find any references to such studies. It is thus not apparent whether the two processes exist as independent and unrelated lesions or whether they are intimately intermingled. Because of the paucity of information on this point the following report of a case is deemed worthy of publication.

REPORT OF A CASE

A white woman 50 years old first began to have asthma at the age of 46 and for the last four years before her death had increasingly more severe and more frequent asthmatic seizures. At first these were easily controlled by injections of epinephrine hydrochloride, but later this drug was less effective. Her last attack started a week prior to her admission to the Jefferson Medical College Hospital, and because administration of both epinephrine and theophylline ethylenediamine did not alleviate her distress she was hospitalized. She was markedly dyspneic, had wheezes over her entire chest and was semicomatose. Caffeine and sodium benzoate U. S. P., epinephrine, theophylline ethylenediamine and oxygen, which was given continuously, were of no avail, and she died of suffocation twenty-four hours after admission.

Roentgenograms of the chest were not made, and the only significant laboratory findings were a leukocyte count of 28,200 cells per cubic millimeter with 90 per cent polymorphonuclear leukocytes and 2 per cent eosinophils, a heavy cloud of albumin in the urine, the presence of acetone and occasional pus cells and granular casts in the urine, and a specific gravity of 1.038. Although cutaneous tests for sensitivity to the common allergens were performed sometime before the last illness and were said to be positive, the record does not contain a list of the substances to which the patient was sensitive.

Necropsy, twelve hours after death, revealed the lungs to be voluminous; they filled the pleural cavities entirely and encroached on the mediastinum anteriorly. Their serosal surfaces were mottled light gray and slate gray and entirely free of adhesions. The lungs were light and feathery, weighing 220 and 460 Gm. respectively. Crepitations were fine and somewhat decreased. Cut surfaces disclosed a soft pinkish gray, rather dry parenchyma wherein the medium-sized bronchi and their subdivisions were conspicuous because, although of normal caliber, they were filled to capacity with thick, sticky, tenacious, light gray, mucoid material that pulled away in long strings. The mucosa of the large bronchi and the trachea was slightly congested, and the lumens contained less mucus than did those of the more distal portions of the bronchial tree. Immediately beneath the pleura and just lateral to the apex of the upper lobe of the left lung there was a firm, sharply circumscribed but not encapsulated nodule of fibrous tissue that measured approximately 1 cm. in greatest diameter. Grossly it contained no evident areas of softening nor did it reveal any tubercles at its periphery. There were no other fibrous or miliary foci in either lung. The mediastinal lymph nodes were anthracotic but otherwise normal. The heart weighed 300 Gm. and the right side showed no hypertrophy. In none of the thoracic or abdominal organs was there any evidence of active tuberculosis. In each maxillary sinus the lining membrane was thickened to as much as 2 mm. across. The nasal mucosa was only moderately thickened. An attempt was made to secure the lining of the sphenoid and ethmoid sinuses through the nose but this was unsuccessful. The brain was not examined.

Routine sections were made of all the thoracic and abdominal organs and in addition numerous sections of the left lung because it was available for reexamination. The lining of the trachea and larger bronchi to an internal diameter of approximately 6 mm. disclosed only those changes typical of bronchial asthma (fig. 1). The lumen contained a varied amount of mucus and debris. The trachea was either partially denuded of its lining epithelial cells or showed islands of fairly normal-appearing cells containing occasional droplets of mucus and in scattered areas covered with cilia. The bronchi showed more denudation, more secretion and a complete absence of cilia. The basement membrane throughout was broad, dense and hyaline. The submucosa showed considerable edema, congestion of the capillaries and a diffuse infiltration of polymorphonuclear leukocytes, plasma cells and lymphocytes. Eosinophils were rather sparse in the trachea but became more numerous as the smaller bronchi were approached until

From the Clinical Laboratories, Jefferson Medical College Hospital.

1. Harkavy, J., and Hebald, S.: Am. Rev. Tuberc. **21**:644, 1930. Sterling, A.: J. Allergy **1**:185, 1929-1930. Laub, S. J.: Illinois M. J. **62**:54, 1932. Fraenkel, E. M.: Brit. M. J. **2**:513, 1934.

2. Locker, A. M., and Davidson, A. G.: J. Allergy **15**:108, 1944.

3. Giffin, H. Z.: Am. J. M. Sc. **142**:869, 1911.

at about the 6 mm. ramifications they constituted the principal type of cell. In all the bronchi the smooth muscle layer was conspicuous. The glands of the submucosa in both the trachea and the bronchi were actively secreting.

Almost all of the bronchi whose internal diameters were less than 5 mm., together with the bronchioles and even the alveolar ducts, were filled with Curschmann's spirals. These consisted of twisted layers of fibrin, mucus, detritus, nuclear fragments, many eosinophils and fewer plasma cells, lymphocytes and recognizable sloughed epithelial cells. The underlying walls of these portions of the bronchial tree disclosed two distinct but intimately intermingled pathologic processes. The first was a diffuse infiltration of the type seen in bronchial asthma, and the second was an acute granulomatous lesion approaching the type seen in the fulminating "soft tubercle" type of tuberculosis. The former consisted of extension and accentuation of the lesion already described in connection with the trachea and larger bronchi (fig. 2). Gradually the epithelial cells showed more and more replacement with large droplets of mucus until in the bronchioles only a few scattered cells were still recognizable as epithelial cells and even these were distorted by an abundant amount of mucoid material. Cilia were not seen. Everywhere the basement membrane was broadened, hyalinized and conspicuous. The rest of the wall was greatly thickened and composed of a background of edematous fibrous and connective tissue wherein the muscle fibers and glands were partially or completely destroyed. Capillaries were engorged and numerous. There was a diffuse and dense infiltration of eosinophils and fewer plasma cells and lymphocytes. Whereas ordinarily this diffuse inflammation was confined to the bronchial and bronchiolar walls, it sometimes extended into the immediately adjoining alveolar septums.

Throughout the walls of about two thirds of the smaller bronchi and bronchioles and extending from the basement membrane to the cartilages and even beyond there was a second, granulomatous type of lesion (figs. 2 and 3). This consisted of many small and fairly uniform-appearing foci composed of a central area of complete necrosis and a surrounding zone of perpendicularly arranged epithelioid cells. While most of the latter were of the ordinary mononuclear variety, a few were grouped together to form rather spurious giant cells consisting of two to four eccentrically or peripherally placed nuclei and an abundance of pink cytoplasm. Immediately surrounding and partly infiltrating the zone of epithelioid cells there were a few plasma cells and lymphocytes, and these were in turn surrounded by varied numbers of eosinophils. The latter blended with the adjoining inflammatory reaction already described. Although most of the tubercles were of the necrotic variety, a few were more solid and in place of the central areas of necrosis disclosed collections of round or oval mononuclear or multinuclear giant cells intermingled with definite epithelioid cells. In most of the smaller bronchi these granulomatous foci were confined to the bronchial walls, but in the bronchioles they were in direct communication with conglomerate foci of an exactly similar nature that infiltrated both the adjoining alveolar walls and the alveolar spaces (fig. 4).

Numerous sections of the apical scar of the left lung disclosed a mass of hyalinized acellular fibrous tissue, which contained scattered deposits of carbon pigment. Along one border this hyalinized mass was covered with rather cellular fibrous tissue, the edges of which contained numerous active tubercles of the type already described (fig. 5). These infiltrated the alveolar septums and spaces and, as in other portions of the lungs, were sometimes seen surrounding bronchioles. Although serial sections were not made, several sections from each block did not disclose any areas of old necrosis or calcification within the fibrous tissue. Sections of other portions of each lung disclosed chronic emphysema alternating with areas of atelectasis. None of the vessels showed recent, old or healed periarteritis nodosa. Only those lymph nodes at the hilus of the left lung were available for histologic study, and none of them showed any evidence of recent or old tuberculosis.

Microscopic sections of the nasal mucosa disclosed a covering of nonciliated, nonsecreting transitional epithelium several cell layers thick. The basement membrane was thick and hyalinized. The glands were numerous and actively secreting and were supported by dense fibrous tissue, which was infiltrated with lymphocytes, plasma cells and scattered eosinophils. Tubercles were not observed. In each maxillary sinus the lining membrane was about ten times the normal thickness. It was mostly denuded of its epithelium, having only a single or a double basilar layer of nonciliated cells (fig. 6). As in the nose, the basement membrane was hyalinized and conspicuous. The submucosa showed marked edema and was heavily infiltrated by eosinophils and fewer plasma cells and lymphocytes. The former were particularly abundant immediately beneath the basement membrane. In this region there were also numerous tubercles of exactly the same structure as those already described in the lungs.

Giemsa-stained sections of the lungs rendered particularly conspicuous the eosinophils and the necrotic foci of the tubercles but failed to disclose any bacteria, fungi or inclusion bodies in any of the lesions. Acid-fast stains of duplicate sections disclosed many acid-fast granules but no tubercle bacilli. Elastic tissue stains with Van Gieson's counterstain showed complete disruption of both the elastic tissue and the muscle bundles in areas involved with the granulomatous process.

Routine sections of the heart, all the abdominal organs and the marrow of the lumbar vertebrae failed to show either tubercles or periarteritis nodosa.

COMMENT

That the patient whose case is described in this report had true bronchial asthma is borne out clinically by (1) the sudden appearance of typical attacks of asthma four years previously which until the last attack were readily and completely controlled with epinephrine and (2) the fact that she was known to be sensitive to some of the commoner allergens, although the exact nature of these was not disclosed in the recorded history. The clinical impression of bronchial asthma is further supported by the rather typical patholgic changes observed in the lungs. Grossly, they were voluminous, light, feathery and dry and the bronchi and bronchioles were filled to capacity with mucous plugs. Microscopically, there were blocking of the lumens of the smaller bronchi and bronchioles with Curschmann's spirals, conversion of the epithelial cells into goblet cells, which were distended with mucus and showed a loss of their cilia, hyalinization and conspicuous widening of the basement membrane, great thickening of the submucosa by edematous connective and fibrous tissue and

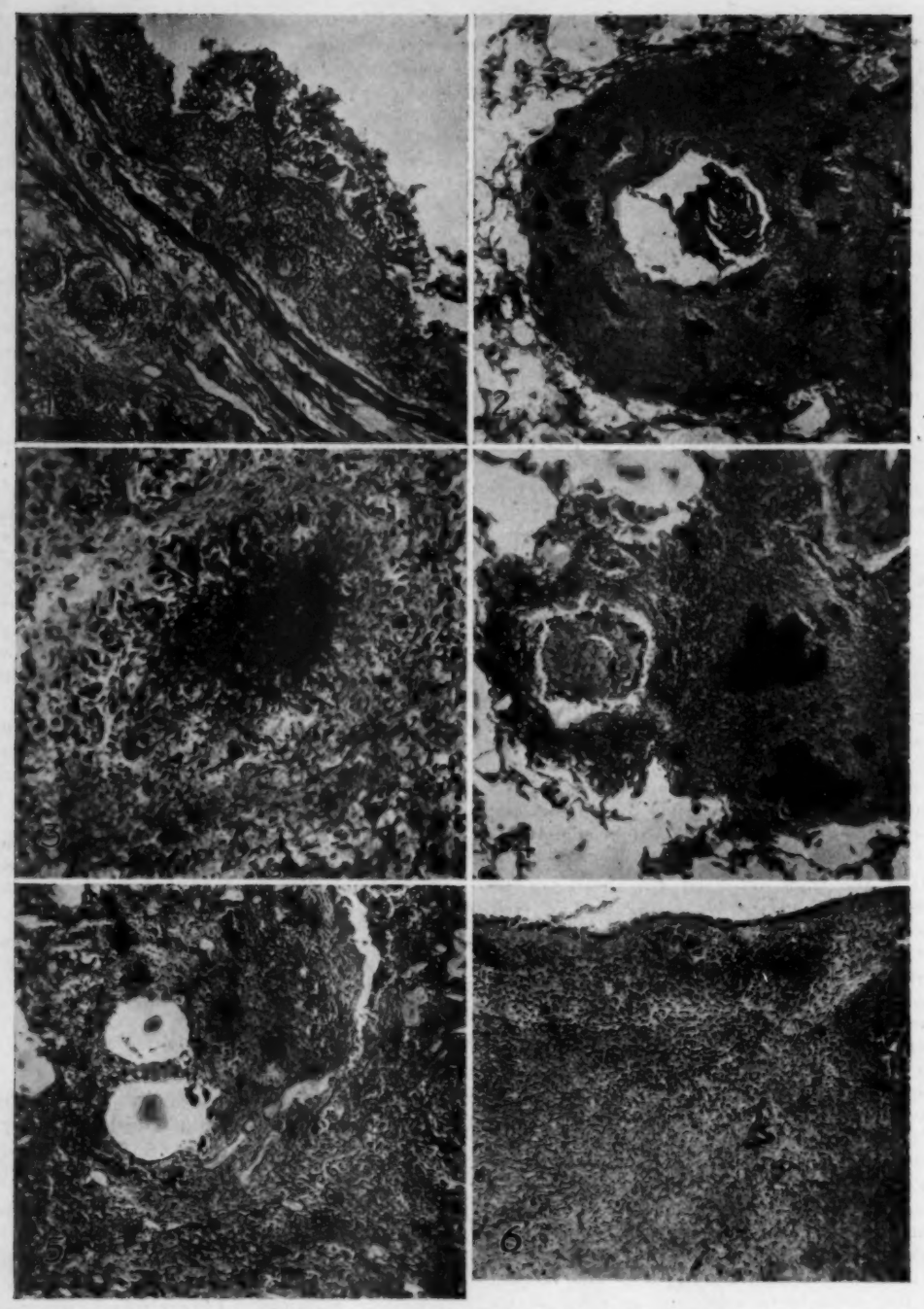


Fig. 1.—Section of a large bronchus in which the lumen contains debris, the wall is partially denuded of mucosa, the remaining epithelial cells are without cilia, the basement membrane is prominent and hyalinized, the submucosa is edematous and congested, with a cellular infiltration in which eosinophils are abundant, and the muscle bundles are prominent. Hematoxylin and eosin; × 75.

Fig. 2.—A small bronchus partially occluded with mucus and detritus. The epithelium that remains contains vacuoles. The entire wall is greatly thickened by asthmatic granulation tissue in which eosinophils predominate and by numerous tubercles. Hematoxylin and eosin; × 25.

Fig. 3.—High magnification of bronchiolar tubercle. Central area of necrosis is surrounded by epithelioid and giant cells. At the periphery are lymphocytes, plasma cells and farther out many eosinophils. Giemsa stain; × 200.

Fig. 4.—Peribronchiolar tuberculous pneumonia with extension of this process to the walls of the bronchioles, which are already involved with a lesion typical of asthma. Hematoxylin and eosin; × 37.5.

Fig. 5.—Section from scar of apex of left lung showing from below up dense scar tissue containing carbon pigment, more cellular fibrous tissue and tubercles along "spreading border." Hematoxylin and eosin; × 37.5.

Fig. 6.—Section of the mucosa of the right antrum showing partial epithelial denudation with loss of the cilia of the remaining epithelial cells, prominence and hyalinization of the basement membrane, congestion and edema of the submucosa and diffuse infiltration by eosinophils. To the right, immediately beneath the basement membrane, there are two small tubercles and a portion of a larger one. Hematoxylin and eosin; × 75.

diffusely infiltrating eosinophils, hypertrophy and hypersecretion of the submucosal glands and hypertrophy of the muscle bundles of the bronchi. These changes in the bronchial mucosa have often been described in the past,[4] and while they are considered as characteristic of bronchial asthma by some authors, they are considered as nonspecific by others.[5] Rackemann[6] has recently stated that if one differentiates between true asthma and asthma-like conditions, particularly in patients in whom asthma develops after the age of 40, one will find that the microscopic changes in the bronchial tree are highly characteristic. To this view I fully subscribe and therefore consider the histologic alterations described in this report as specific for the disease.

What applies to the mucosa of the tracheobronchial tree applies equally to the mucosa of the nasal and paranasal sinuses of asthmatic patients. Unfortunately, permission to examine the head and so the sphenoid, ethmoid and frontal sinuses was not granted, but it is reasonable to assume that the changes in these membranes were similar to those seen in the mucosa of the maxillary sinuses. It is rather surprising that, although histologic studies of the mucosa of the nasal and paranasal sinuses[7] and of the trachea, bronchi and bronchioles have been made independently on many occasions, both parts of the respiratory tract have seldom been studied in the same patient.[8] In the case reported here it is clearly seen that the lesion of the upper portion of the respiratory tree is so similar to that of the lower portion that one could almost be superimposed on the other.

The diagnosis of tuberculosis in this case was based entirely on the histologic appearance of the granulomas. The peripheral collections of epithelioid and giant cells surrounding either central foci of eosinophilic necrosis or more densely arranged epithelioid and giant cells appeared to be midway between the "soft" and the "hard" tubercles described by Rich.[9] The one disturbing factor was the failure to demonstrate any definite tubercle bacilli which Rich maintained is easy to do in the "soft" tubercles. This failure may be explained by the fact that even the most recent tubercles were not as acute as the "soft" tubercles referred to, as evidenced by the always present zone of epithelioid cells and scattered giant cells. In such lesions one would expect fewer tubercle bacilli and so more difficulty in demonstrating them. Acid-fast granules, however were present in most of the necrotic centers. Because the lesion was not suspected at the time of necropsy, cultures for tubercle bacilli and inoculations of guinea pigs were not carried out. Since "soft" tubercles, which the lesions here approach, are found only in hypersensitive persons, the disease as described was a result of a reinfection, and the primary tuberculous focus was represented by the apical scar in the upper lobe of the left lung. Although a central area of caseation, such as those which are sometimes seen to persist in such scars, was not noted, the spreading edge of this fibrous nodule[9] was quite characteristic of a relighted tuberculous lesion.

The exact mechanism by which the tuberculous process was disseminated throughout the respiratory system is difficult to ascertain with any degree of certainty. There are three observations, however, that point to an air-borne spread. First, the infection was limited to the respiratory passages alone and was not found in the intervening parenchyma of the lung. If the dissemination had been blood borne, one would expect to find it throughout all portions of the lungs if a pulmonary artery was eroded, or throughout the entire body if the bacilli gained entrance into a pulmonary vein. Second, the distribution of the tubercles was typical of that seen with an air-borne spread, namely, the presence of small foci of tuberculous pneumonia beyond and about the bronchioles and alveolar ducts with a subsequent secondary involvement of the walls of these terminal portions of the bronchial tree.[9] Third, however common pulmonary tuberculosis is, it is unusual to find tuberculosis of the paranasal sinuses.[10] The presence of tubercles in the superficial portions of the mucous membranes of each antrum, that is, just beneath the basement membrane, bespeaks air-borne infection, for had it been blood borne the lesions would not only have been in the deeper portions of the submucosa but, as already stated, in the other organs of the body as well. Although the source of the aerogenous reinfection was not absolutely divulged, it was probably a reanimated focus in the upper lobe of the left lung. Because, however, an area of old necrosis was not seen in that "healed" lesion, the following two alternate sources may be mentioned: (1) another more active focus in the

4. (*a*) Huber, H. L., and Koessler, K. K.: Arch. Int. Med. **30**:689, 1922. (*b*) Kountz, W. B., and Alexander, H. L.: Arch. Path. **5**:1003, 1928. (*c*) Thieme, E. T., and Sheldon, J. M.: J. Allergy **9**:246, 1938. (*d*) Michael, P. P., and Rowe, A. H.: ibid. **6**:150, 1934. (*e*) MacDonald, I. G.: Ann. Int. Med. **6**:253, 1932. (*f*) Hilding, A. C.: Ann. Otol., Rhin. & Laryng. **52**:5, 1943.

5. (*a*) Tuft, L.: Clinical Allergy, Philadelphia, W. B. Saunders Company, 1937, p. 327. (*b*) Lamson, R. W.; Butt, E. M., and Stickler, M.: J. Allergy **14**:396, 1943.

6. Rackemann, F. M.: Arch. Int. Med. **73**:248, 1944.

Lamson and others.[5b]

7. Semenov, H.: J. A. M. A. **111**:2189, 1938. Grove, R. C.: New York State J. Med. **41**:455, 1941.

8. Kountz and Alexander.[4b] Michael and Rowe.[4d]

9. Rich, A. R.: The Pathogenesis of Tuberculosis, Springfield, Ill., Charles C Thomas, Publisher, 1944, pp. 819, 856 and 852.

10. Hersh, J. H.: Arch. Otolaryng. **28**:987, 1938. Radner, D. B., and Pinkerton, F. J.: Am. Rev. Tuberc. **50**:313, 1944.

right lung which was not found but which had discharged its contents into a bronchus and (2) an entirely new exogenous infection.

Since the patient had both asthma and tuberculosis, the final question to be answered is the extent to which the tuberculosis contributed to the asthmatic attacks. From a consideration of both the clinical and the pathologic data it is apparent (1) that the asthma was the initial and older lesion and that the tuberculosis was only more recently superimposed, (2) that because the two lesions were so intimately intermingled the diameters of the terminal portions of the bronchial tree were narrowed not only by the asthmatic granulation tissue but by the tubercles as well, and therefore in this manner each contributed to the obstruction and the dyspnea, and (3) that in the areas of tuberculous involvement the muscle bundles in the walls of the bronchi and bronchioles were completely disrupted by the tubercles. Although it is known that in status asthmaticus epinephrine [5a] may have little or no beneficial effect, the lack of response to this drug in the case reported here may have been related to the destruction of the muscle fibers. While muscle spasm in the larger bronchi, where the bundles were intact, undoubtedly contributed to the severity of the asthmatic attacks and was probably relieved by the epinephrine, such relief was not possible in the more peripheral portions, where the muscles were destroyed and the occlusion was due entirely to mucous plugs and thickening of the wall by cellular infiltration.

SUMMARY

That bronchial asthma and tuberculosis can occur concomitantly in the same patient is well established, but the morphologic relationship of the two diseases is not apparent from a review of the literature. In the case presented a patient 50 years old who died in status asthmaticus and in whom asthma had developed four years previously was found on histologic examination to have in the mucosa of the upper and lower respiratory tree an intimate intermingling of asthmatic granulation tissue with tuberculous lesions. It is concluded, therefore, that the latter can contribute appreciably to the occlusion of the air passages and so to the asthmatic attacks.

General Reviews

NEOPLASTIC DISEASES OF THE HUMAN HYPOPHYSIS

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PEORIA, ILL.

THE ADENOMA

The enormous amount of literature on this topic proves the frequency of tumor formation in the hypophysis. In 1914 Kraus,[1] after examining 300 hypophyses in serial sections, stated that 25 glands were involved by adenoma, while 13 showed adenomatous hyperplasia. Among 1,000 unselected persons Castello[2] encountered adenoma of the hypophysis in about 1 of every 4 cases. The greatest incidence of adenoma occurred in persons in the sixth decade of life; males and females were involved about equally. Among 50 cases of primary tumor of the hypophysis Puestow[3] found adenoma in 60 per cent, in 15 per cent of which it was carcinomatous. According to Kraus,[1] adenoma involves the hypophysis in 30 per cent of persons from 50 to 60 years of age, in 15 per cent of persons from 30 to 50 and only in 6 per cent of persons below 20 years of age. Ecker[4] investigated the frequency of small basophilic adenoma and found it in 54 of 721 hypophyses. The frequency of chromophobe, chromophil and mixed adenoma was examined by Bailey,[5] who observed that the chromophobe type was three times more frequent than the two chromophil types. The incidence of adenoma and craniopharyngioma as compared with other intracranial blastomas becomes evident from Bailey's statistical work, based on 2,000 cases. According to Bailey hypophysial adenoma represents 17.8 per cent and craniopharyngioma 4.3 per cent of all intracranial tumors. A similar result was obtained by Henderson,[6] who observed hypophysial adenoma in 17 per cent of all persons with tumor of the brain.

The anatomic picture of hypophysial adenoma varies greatly. While in some instances it is tiny and thus macroscopically hardly discernible, in others there is present a huge tumor mass protruding from the enormously enlarged sella turcica and destroying the neighboring parts of the brain and the cranial base by pressure or infiltration or both. As long as it does not exceed a certain size, its growth takes place predominantly in the lateral direction and downward toward the bottom of the sella, since the diaphragm of the sella withstands the abnormal pressure longer than the osseous wall of the sella. With the adenoma growing larger, the entrance to the sella gets wider, and the tumor projects through the diaphragm into the cranial space. Thus an extrasellar portion of the tumor arises which sometimes considerably exceeds in size the intrasellar portion. The two portions, the intrasellar and the extrasellar, in typical cases are differentiated by a circular ring of constriction giving an hourglass shape to the tumor. The larger growth may invade one or both cavernous sinuses, extend to the carotid vessels, destroy the sella and break into the sphenoid and ethmoid sinuses and even into the nasopharynx and the maxillary sinuses (Cushing[7]; Bailey and Cutler[8]; Spark and Biller[9]). A tumor extending posteriorly destroys the dorsum sellae and the clivus; a tumor may penetrate the dura, grow outside the dura along the blood vessels and reenter the subdural space, forming nodules on the inner surface of the dura. Growing toward the foramen opticum, the adenoma may invade the orbits.

Growing toward the brain, the adenoma comes into contact with this organ below, behind or in front of the optic chiasm. This is pushed upward and becomes flattened, together with the optic tracts and the optic nerves. The optic nerves become atrophic, sometimes constricted and even severed as a result of pressure against the medial cerebral artery or other branches of the circle of Willis. In rare instances the chiasm is perforated by the tumor. In its further growth, the adenoma burrows more and more deeply into the diencephalon, causing atrophy and destruction of the floor of the third ventricle. With

From the Department of Pathology, St. Francis Hospital.

1. Kraus, E. J.: Beitr. z. path. Anat. u. z. allg. Path. **58**:159, 1914.
2. Castello, R. T.: Am. J. Path. **12**:205, 1936.
3. Puestow, C. B.: Arch. Neurol. & Psychiat. **22**:547, 1929.
4. Ecker, A. D.: Endocrinology **23**:609, 1938.
5. Bailey, P.: Tumors of the Hypophysis Cerebri, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1131.
6. Henderson, W. R.: Brit. J. Surg. **26**:811, 1939.
7. Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C Thomas, Publisher, 1932.
8. Bailey, O. T., and Cutler, E. C.: Arch. Path. **29**:368, 1940.
9. Spark, C., and Biller, S.: Arch. Path. **35**:93, 1943.

a larger tumor the peduncles, occasionally the temporal lobes and rarely the frontal lobes are pushed apart and compressed by portions of the tumor. Sometimes the tumor breaks through the floor of the third ventricle and projects into the greatly dilated ventricle, pushing apart the thalami optici and corpora striata and crowding out the fornix and the corpus callosum. The tumor may not only displace these structures but infiltrates them. The question to what extent expansive, and to what extent infiltrative, growth has participated in the destruction of the adjacent parts is sometimes macroscopically hard to determine. Experience shows that even with cancerous adenoma the destruction is due more to the pressure exerted by the tumor than to infiltration.

Besides the optic nerves, other nerves adjacent to the tumor, such as the oculomotor and trochlear nerves, less frequently the abducent or trigeminal nerves, are crowded out, stretched and flattened. Thus paralysis of ocular nerves is not rare, as is shown by Weinberger, Adler and Grant,[10] who, among 160 cases of adenoma of the hypophysis, noted 14 in which paralysis of ocular nerves dominated the clinical picture (cavernous sinus syndrome).

The injury done by the adenoma to the remainder of the hypophysis varies in severity. Even in some cases of adenoma of large size the hypophysis, lying at the base of the deepened sella, may be in a fairly good condition, whereas in other cases the hypophysis is destroyed or reduced to a flat, atrophic structure. Concentrically arranged layers of atrophic cells forming a thin shell frequently are found surrounding the basal parts of the tumor. In case of predominantly extrasellar growth, the hypophysial stalk becomes destroyed at an early stage of the advance. In the vast majority of cases adenoma arises from the anterior lobe. Basophilic adenoma springs from both the anterior and the posterior lobe. Occasionally the origin of adenoma can be traced to foci of anterior lobe parenchyma dispersed along the craniopharyngeal canal within the sphenoid bone. If the adenoma is eosinophilic in nature, acromegaly may result.[11] In rare instances adenoma starting from the pharyngeal hypophysis has been recorded. It is represented by a retropharyngeal mass between the pharynx and the spine.[12]

Though adenoma of the hypophysis frequently is carcinomatous, metastases are seldom observed. Multiple metastatic nodules in the leptomeninges, even as far as the cauda equina, have been seen. Extension of a carcinomatous adenoma up to the occipital foramen, with the tumor breaking into the pons, the medulla and the bulbus venae jugularis, with metastases to the lungs and the pleura, has also been observed. An eosinophilic adenoma with metastases to the skeleton has been described by Vasiliu[13]; a carcinoma with abdominal metastases, by Gilmour.[14]

There are as many types of hypophysial adenoma as there are cell types in the hypophysis. The histogenesis of these tumors is expressed by placing before "adenoma" the name of the cell type from which the adenoma has originated. Thus one speaks about chief cell adenoma, fetal cell adenoma, pregnancy cell adenoma, eosinophilic adenoma and basophilic adenoma. When more than one cell type is represented in the adenoma, the tumor is called mixed cell adenoma. Mixed cell adenoma is composed of (1) chief cells and transitional cells, (2) these cells together with chromophilic cells, (3) transitional and chromophilic cells and (4) fetal cells and chief cells. The term "malignant adenoma" is used oftener than the term "carcinoma" in order to emphasize the difference which exists between these tumors and ordinary carcinoma. It should be borne in mind that the cells in carcinomatous adenoma are not always differentiated enough enough to reveal their true histogenesis. For instance, in the cases of carcinomatous adenoma without demonstrable specific cell granules, the term "carcinomatous chromophobic adenoma" might be used. It also should be mentioned that the tumor cells in old eosinophilic adenoma may lose their specific granules to such an extent that unless examined by specific methods thoroughly, the eosinophilic character of the adenoma may be overlooked. This might have happened in some cases of "acromegaly without eosinophilic adenoma."

While eosinophilic and chromophobic forms of adenoma seem to arise almost exclusively in the anterior lobe, basophilic adenoma is found, as said, in the anterior as well as in the posterior lobe—in the former, however, much more frequently than in the latter. In Cushing's disease it has been seen in either lobe. Crooke's "hyalin change" of the basophilic cells, supposedly characteristic of Cushing's disease, was noted by Ecker[4] in 5.5 per cent of cases of basophilic

10. Weinberger, L. J.; Adler, F. H., and Grant, F. C.: Arch. Ophth. **24**:1197, 1940.

11. Erdheim, J.: Beitr. z. path. Anat. u. z. allg. Path. **46**:233, 1909.

12. Leegard: Norsk mag. f. lægevidensk. **78**:829, 1917.

13. Vasiliu, T.: Virchows Arch. f. path. Anat. **276**: 141, 1930.

14. Gilmour, M. D.: J. Path. & Bact. **35**:265, 1932.

adenoma without Cushing's disease, whereas in the rest of the cases the hypophysis was free of any such change. Ecker, of course, in these cases missed ballooning of the nuclei, excessive vacuolation, tendency to multinucleation and general enlargement of cells. It may be mentioned here that basophilic adenoma, as a rule, does not attain the size of chromophobic or eosinophilic adenoma.

There is one type of chromophobic adenoma in which the cells are similar in shape and arrangement to those in the anterior lobe during the very early stage of fetal life. For this reason, Kraus,[1] who described the tumor first in 1914, called it fetal or fetal cell adenoma, since he assumed that it originated from remnants of these fetal cells, which are sometimes found in the anterior lobe. These tumors are characterized by high cylindric or fusiform cells arranged in bandlike interlacing strands. Thus arise cell palisades which, resting on the septums and the capillary walls, confer on the new growth a characteristic appearance (Kraus [15]; Berblinger [16]; Shapiro [17]). Circumscribed hyperplasia, as well as circumscribed nodules made up of these cells, are not rare. Usually the nodules are small; however, in a case reported by Kraus the tumor was the size of a hazelnut and infiltrated the hypophysial capsule as well as the adjacent parenchyma. In carcinomatous types, diffuse proliferation of the tumor parenchyma without particular cell arrangement may be seen in some parts while the characteristic picture described is seen in other parts.

Another rare type is the so-called pregnancy cell adenoma which, as the name indicates, is made up of cells morphologically corresponding to the normal pregnancy cells These little nodules represent more a form of adenomatous hyperplasia than real adenoma. The structure of the hypophysial adenoma varies, with the cells taking an alveolar or a perivascular or a diffuse arrangement; adenoma with papillary and in rare instances cylindromatous structures [18] also may be seen.

The adenoma in the hypophysis sometimes seems to spring from a local cell hyperplasia showing a well defined contour only on one side, whereas on the other side the cells proliferate diffusely, merging into the adjacent hypophysial parenchyma. To outline the new growth from the neighboring cells in places where a distinct margin is missing, fat stains with osmium or sudan are used to differentiate the newly formed tissue from the normal parenchyma. The new growth shows a lack of lipoids as compared with the considerable lipoid content of the normal tissue. Such a nodule, partly without sharp outlines, is called adenomatous hyperplasia. It is not rare, especially in the posterior lobe, where it is made up of basophilic cells, evidently springing from the basophilic cells normally present in the posterior lobe.

The question as to whether the chromophilic adenoma originates from chief cells or exclusively from chromophilic cells has been discussed often. The fact that in some cases chief cells are present together with chromophilic cells, linked by transitional cells, seems to indicate that in at least some cases chromophilic adenoma springs from chief cells which by further differentiation turn into chromophilic elements. It is allowable, however, to assume that chromophilic adenoma also arises directly from chromophilic cells as, for instance, in the posterior lobe, where basophilic adenoma may be seen emerging from the basophilic cells regularly found in this part of the organ.

In some instances it might be difficult to distinguish microscopically between simple and cancerous adenoma. When infiltrative growth can be proved, there cannot be any doubt of carcinoma. The presence of granules in the cells, although these cells may show high differentiation, is no proof of simple adenoma. The most reliable sign of carcinoma aside from infiltrating growth is anaplasia of the tumor cells, characterized by irregularity in size and shape of cells and nuclei and by particularly large size of the latter, which exceed the size of nuclei in adenoma. While alveolar arrangement of the tumor cells is usually noted in adenoma, a more diffuse arrangement suggests carcinoma. In instances of cancerous adenoma, the formation of cell strands is maintained, but these are broader than those in adenoma. The frequently observed perivascular arrangement of the tumor parenchyma is also suggestive of carcinoma. This perivascular arrangement has caused, especially in older publications, misinterpretation of adenoma as, for example, perithelioma, perivascular sarcoma or angiosarcoma.

Infiltrative growth of basophilic adenoma in the posterior lobe is not always a reliable criterion of carcinoma. This adenoma springs from the basophilic cells, which physiologically invaded the posterior lobe by infiltration. They may maintain this behavior, which of course does not prove that the growth is carcinoma, at least

15. Kraus, E. J.: The Hypophysis, in Henke, F., and Lubarsch, O.: Handbuch der pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 810.

16. Berblinger, W.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1932, vol. 1, p. 910.

17. Shapiro, P. F.: Arch. Path. **11**:22, 1931.

18. Jedlička, V.: Sborn. lék. **25**:149, 1924.

as long as it remains confined to the posterior lobe; only after it has invaded other structures, can carcinoma be diagnosed. In some instances adenoma turns into carcinoma—an incident that as far as the eosinophilic adenoma is concerned, according to Spark and Biller,[9] occurs in about 20 per cent of the cases.

Retrogressive lesions in cases of hypophysial adenoma are not rare. They are chiefly necrosis, hyaline degeneration of the interstitial tissue and formation of hyaline concentric-layered bodies with or without calcification. An adenoma with calcareous concretions is called struma calculosa or adenoma psammosum. Calcification may also occur in the form of amorphous, irregularly shaped calcium deposits. Several times petrified adenoma has been described as stone-hard in consistency and coarsely granulated on the cut surface (Kraus[18]). The microscopic picture may show numerous round psammous bodies, as those in the choroid plexus, closely approximated, with little tumor parenchyma left between them. Psammous adenoma can be suggested from the roentgenogram, which discloses a shadow within the tumor (Deery[19]). The same features, of course, are seen more often in old forms of craniopharyngioma which undergo calcification.

Among the circulatory lesions in adenoma, hemorrhages are most common. In rare instances the whole adenoma may undergo hemorrhagic infarction, apparently due to thrombosis or perhaps compression of veins. An old hemorrhage may become encapsulated and form a hemorrhagic cyst. Trauma may be the inciting cause of a hemorrhage in the tumor, as has been shown by Van Wagenen.[20] Edema (together with slight fibrosis) was seen by Goldberg and Lisser[21] in an eosinophilic adenoma after it had been irradiated with roentgen rays.

To determine the site of origin of adenoma is possible only when the tumor is small. The chief cell adenoma and the adenoma made up of transitional cells prefer the peripheral parts of the anterior lobe; the small pregnancy cell adenoma affects the lateral parts, occurring especially in the corner between the border of the posterior lobe and the lateral portion of the capsule of the anterior lobe. The eosinophilic adenoma lies more in the central part and the basophilic adenoma in the central part but close to the posterior lobe or in the posterior lobe itself. The fetal cell adenoma is found in both the central and the peripheral parts of the anterior lobe.

Hypophyses with adenoma sometimes show small so-called hernias, gaps up to 1 mm. in width, in the capsule of the anterior lobe. These contain prolapsed parenchyma, may be single or multiple and arise apparently where vessels pass through the capsule. Increased pressure within the hypophysis may cause these small ruptures.

THE CRANIOPHARYNGIOMA

The tumor second in frequency to the adenoma is the craniopharyngioma, which is derived from the squamous epithelium of the former craniopharyngial canal. In many cases small groups of these cells are found in the anterior and superior parts of the anterior lobe of the hypophysis as well as in the pars infundibularis. When the craniopharyngioma springs from cell groups dispersed into the anterior lobe, an intrasellar craniopharyngioma develops; when it arises from cell groups in the pars infundibularis, the result is a suprasellar craniopharyngioma. While craniopharyngioma in this location, especially above the sella, is not rare, only a few cases are known in which the tumor developed within the sphenoid bone, in the region of the former craniopharyngial canal proper (Zeitlin[22]). Why just the intrasphenoid craniopharyngioma appears to be so rare can be explained only by the fact that the epithelial remnants of the craniopharyngial canal do not persist within the bone with the same frequency as in the aforementioned parts of the hypophysis.

There are simple and carcinomatous forms of craniopharyngioma, partially solid, partially cystic or cystic-papillary in structure. In many cases both solid and cystic parts are seen. These tumors vary greatly in size, attaining in rare cases the size of a man's fist. The intrasellar craniopharyngioma crowds out the hypophysis, causing extreme atrophy and widens and deepens the sella. Growing larger, it projects out of the sella and displaces the neighboring diencephalon upward. It may destroy the sella and even larger parts of the sphenoid bone as far as the pharyngeal wall, pushing the latter downward. Growing toward the optic chiasm, it usually invades the brain in front of the chiasm. Nodular portions of the craniopharyngioma can break into the lateral ventricle and into the frontal lobes. If the craniopharyngioma is cancerous, it infiltrates the adjacent parts of the skull and the brain and sometimes sets up metastases to the brain. Occasionally a can-

19. Deery, E. M.: Endocrinology **13**:455, 1929.

20. Van Wagenen, W. P.: Ann. Surg. **95**:625, 1932.

21. Goldberg, M. B., and Lisser, H.: J. Clin. Endocrinol. **2**:477, 1942.

22. Zeitlin, H.: Am. J. Cancer **23**:729, 1935.

cerous craniopharyngioma breaks through into the pharynx after it has penetrated the cranial base along the blood vessels and nerves. Metastatic nodules have been found in the ependyma of the fourth ventricle and may simulate large ependymal granulations Metastases to the cervical lymph nodes also have been described.

Different pictures result when the craniopharyngioma springs from the infundibular part of the hypophysis (outside the sella turcica). It then lies within the circle of Willis and behind the optic chiasm and is attached above to the base of the brain and below to the hypophysis. The floor of the third ventricle is pushed upward and is often extremely thinned or even destroyed, with the result that a large part of the tumor lodges within the ventricle. Sometimes the hypophysis is about normal, but more often it is compressed. The circle of Willis may be lifted and stretched by the tumor; the optic nerves may be indented by one of the arteries and pressed between the growing tumor and the big arteries or they may even be severed.

Histologically, craniopharyngioma is characterized by typical prickle cells, which lack keratohyaline granules as well as cornification. The solid parts of the tumor are made up of squamous cell nests closely approximated and embedded in a fibrous stroma; only the periphery of these cell nests is built by a single layer of cylindric epithelium. Frequently there are regressive changes in both parenchyma and stroma, particularly hydropic degeneration, which by liquefaction often causes pseudocysts. It is believed that the liquefaction is due to poor nutrition of the tissue from hyaline degeneration of the blood vessels.

If the whole cell nest is liquefied, the necrotic mass, stained red by eosin, lies amid the stroma, often surrounded by foreign body giant cells, or else it undergoes calcification. The craniopharyngioma may contain bone tissue which has developed from these calcified foci by metaplasia.[23] Deposits of hemosiderin and cholesterol crystals also are found in specimens of this tumor. The presence of bone and brown pigment, the latter interpreted as melanin, has led to confusing craniopharyngioma with teratoma.

In cystic and cystic papillary craniopharyngioma the lining of the cysts is made up of two or more layers of epithelium, occasionally flattened by the cyst content. The lining shows a basal cell layer and layers of prickle cells, but without keratinization. Characteristic are shaggy vegetations budding from the wall, being attached to it either by a broad base or by thin stalks forming cauliflower-like structures. The papillae are covered by multilayered squamous epithelium and sometimes have an edematous stroma rich in blood vessels. Destruction of the epithelial lining by necrosis, presence of foreign body giant cells, deposition of calcium and cholesterol and ossification are found in the cystic type as well as in the solid type. The cystic content may be colorless, yellow brownish or brown-green; it may be serous, mucous or gelatinous in nature and sometimes shows a large amount of glittering cholesterol crystals. Characteristic of craniopharyngioma is its resemblance to adamantinoma, which has caused many authors to call craniopharyngioma adamantinoma. Finally it is quite typical of craniopharyngioma that the carcinomatous type occurs more often in young persons, whereas the simple form usually is found in older ones. The two sexes are about equally involved.

23. Critchley, M., and Ironside, R. N.: Brain **49**:437, 1926.

OTHER PRIMARY TUMORS

Little fibromas have been seen in the hypophysial stalk as well as in the hypophysis proper. Jedlička[18] has described a fibroma the size of a pea in the pars intermedia together with a partially patent craniopharyngial canal in a 14 year old child with macrosomia. Hemangioma of the anterior lobe and lipoma of the posterior lobe are rare. A hypophysial chordoma was observed by Goerke.[24] A few instances of sarcoma of the hypophysis have been described, such as the instance of fibrosarcoma reported by Willis.[25] Many cases of sarcoma (angiosarcoma, round cell sarcoma, perithelioma and others) described in the old literature were misinterpreted instances of chromophobic adenoma. Glioma and ganglioneuroma of the posterior lobe are mentioned in the literature several times. Globus[26] gave the name "infundibuloma" to a tumor of the hypophysial stalk duplicating the histologic appearance of the neurohypophysis. Globus observed the tumor in children.

Teratoma also belongs to the rare tumors of the hypophysis or hypophysial region. The hypophysis may be found compressed and atrophic beside the tumor. The craniopharyngial canal may be patent, as in a case reported by Gautier,[27] in which the teratoma developed close to the cranial opening of the canal, penetrated the anterior lobe and grew into the third ventricle. In the cases examined, colloid-filled

24. Goerke, M.: Folia oto-laryng. **20**:9, 1930.
25. Willis, R. A.: M. J. Australia **1**:287, 1930.
26. Globus, J. H.: J. Neuropath. & Exper. Neurol. **1**:59, 1942.
27. Gautier: Frankfurt. Ztschr. f. Path. **19**:247, 1916.

cysts, teeth, bone, cysts lined with ciliated epithelium, fat tissue, blood vessels, glia, ganglion cells and other structures have been observed. In other cases anlage material of almost all organs was found. In fetuses and newborn infants complicated teratoma containing fetal parts has been observed in connection with epignathus. Usually there is an intracranial portion in the sellar region in connection with a tumor mass protruding from the mouth, both parts being linked by a narrow middle part running through a defect in the sphenoid bone. Thus the whole tumor assumes the characteristic shape of an hourglass (Baart de la Faille [28]; Kraus [29]). A specimen described by the latter showed a teratoma composed mainly of anlage material of the brain and the eye with islands of cartilage and other mesodermal derivatives. Berblinger [16] in his monograph cited a case reported by du Marchie Sarvaas [30] in which in a boy 12 years of age a huge teratoma had destroyed the hypophysis and the sella and penetrated into the nasal cavity. The tumor contained bone, cartilage, various gland formations (among them mucous glands), glia and other tissues.

Cholesteatoma has been described several times, though it seems not to occur in the hypophysis itself but in the infundibular region. It is of epidermal origin as proved by the presence of keratohyaline granules, which are not found in craniopharyngioma. In a case recorded by Kraus [31] there was a cholesteatoma (the size of a hazelnut) lodged in the angle between the hypophysial stalk and the upper surface of the anterior lobe, the latter not being involved by the tumor. In other cases a cholesteatoma developing at the base of the brain may take the form of a large tumor obliterating the hypophysis.[32]

True cysts of the hypophysis are not frequent. The macroscopic distinction from cystic craniopharyngioma may be difficult to determine in some cases. For instance, a cyst derived from the pars intermedia grossly may simulate cystic craniopharyngioma. Remnants of anterior lobe tissue lining the cyst facilitate the histologic diagnosis. In most of the cases the cyst of the pars intermedia is intrasellar and separates the two lobes. It can be lined by ciliated and also squamous epithelium (Fulstow [33]; Jedlička [18]). A tumor in the region of the sella turcica which was lined with ciliated epithelium was described by Frazier and Alpers [34] and interpreted as a true tumor of Rathke's cleft. In some instances the cyst is not followed by clinical symptoms; in some, however, it has been observed to cause Simmonds' disease, testicular atrophy (Jedlička [18]) and other pathologic changes. Whether or not there are clinical symptoms depends on the size of the cyst and the degree of compression and atrophy of the hypophysis itself The size of the cyst varies from case to case; in the majority it is not large. The size in a case described by Jedlička, 5 by 3.8 by 3.4 cm., must be regarded as a rare size.

Another type of cyst is the ependymal cyst, usually located within the infundibulum and lined by ependyma. Rarely it becomes larger in size than in a case described by Jedlička in which it developed in the infundibulum, passed through the hypophysial stalk and the diaphragm of the sella into the sella and caused marked pressure atrophy of the hypophysis without, however, causing any endocrine symptoms.

METASTATIC TUMORS

Metastatic carcinoma is found more frequently in the hypophysis than metastatic sarcoma. The most frequently observed metastases are derived from carcinoma of the breast, the lung, the bronchial tree and the thyroid gland, but records show that carcinoma of the stomach, the prostate, the kidney and other organs also metastasizes to the hypophysis. According to Wohlwill,[35] who thoroughly examined 177 persons with carcinoma, hypophysial metastases are rare; they occurred in only 5 persons. Metastatic carcinoma in the majority of cases first involves the posterior lobe, from which it often extends to the adjacent parts of the anterior lobe. In some instances the entire hypophysis is destroyed by cancer. The anterior lobe is the primary site of the metastasis less frequently than the posterior lobe. There can be a diffuse carcinomatous infiltration of the anterior lobe while the posterior lobe contains several small nodules. Nodular metastases of carcinoma in the anterior lobe are rare. Carcinoma of the prostate usually invades the sella first and then progresses into the hypophysis. Carcinoma of the nasopharynx or of the sphenoid sinus invading the hypophysis was observed by me in a few instances. When

28. Baart de la Faille, cited by Kraus.[15]

29. Kraus, E. J.: Virchows Arch. f. path. Anat. **271**: 546, 1929; in Schwalbe, E.: Morphologie der Missbildungen des Menschen und der Tiere, edited by G. B. Gruber, Jena, Gustav Fischer, 1929, vol. 3, p. 32.

30. du Marchie Sarvaas, G. J.: Frankfurt. Ztschr. f. Path. **40**:210, 1930.

31. Kraus, E. J.: Med. Klin. **20**:1290 and 1328, 1924.

32. Krumbhaar, E. B.: M. Clin. North America **5**: 927, 1921. Kraus.[15]

33. Fulstow, M.: Am. J. Path. **4**:87, 1928.

34. Frazier, C. H., and Alpers, J. B.: Arch. Neurol. & Psychiat. **32**:973, 1934.

35. Wohlwill, F.: Deutsche Ztschr. f. Nervenh. **105**: 62, 1928.

mainly involving the posterior lobe, metastatic carcinoma may be a cause of diabetes insipidus. Carcinoma of the bronchi, the breast, the thyroid gland and the stomach are the most common types to metastasize thus. Wohlwill [35] pointed to the interesting fact that in many cases of advanced carcinoma (in 45 among his 177 cases) the patient shows an unexpected well developed panniculus adiposus. This can be explained partly by changes in the endocrine system and the vegetative centers in the diencephalon. In 27 of Wohlwill's cases it was his opinion that the cachexia associated with tumor was prevented by the atrophy of the ovaries and the destruction of the hypophysis and the floor of the third ventricle by metastatic tumor.

Besides metastatic carcinoma, metastatic lymphosarcoma, mesothelioma of the pleura and melanoblastoma are mentioned in the literature several times. Cell emboli of melanoblastoma caught in capillaries of the anterior lobe have been observed by me. In a case of primary melanosarcomatosis of the leptomeninges I noted infiltration of the hypophysial stalk. Metastatic sarcoma usually invades the hypophysis after it has destroyed the sphenoid bone. Hematogenous metastasis of sarcoma as recently reported by Kraus [36] in a case of primary sarcoma of the ureter occurs less often than extension of sarcoma, as from the base of the skull or from the pharynx (Jedlička [15]) or from the dura or the brain, to the hypophysis. Such extension may cause diabetes insipidus (Berblinger)[16] or adiposogenital dystrophy. Worms and Delater,[37] however, reported a case in which there was complete destruction of the hypophysis by a nasopharyngeal lymphosarcoma without any symptoms of hypophysial insufficiency. It is also known that diabetes insipidus resulting from a metastasis in the posterior lobe may disappear after the tumor has invaded and destroyed the anterior lobe.

36. Kraus, E. J.: Urol. & Cutan. Rev. **48**:522, 1944.
37. Worms and Delater: Rev. neurol. **32**:361, 1925.

Book Reviews

Bronchial Asthma. By Leon Unger, B.S., M.D., assistant professor in the department of medicine, Northwestern University Medical School, Chicago. Pp. 724, with 123 illustrations. Price $9. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

It is now about twenty-five years since the intensive study of bronchial asthma as an allergic disease began. This book by a pioneer clinician in this special field presents the advances in the understanding, the prevention and the treatment of asthma during that time. The first and longest section deals with the clinical side of allergic asthma—the causes, the pathologic appearances, the symptoms, the diagnosis, the prevention and the treatment. There are chapters also on other allergic diseases and on the military aspects of asthma and other allergies. The historical chapter with its interesting portraits is noteworthy. The second section describes the preparation of the various allergenic extracts used in testing and treatment. The appendix contains a mass of useful information about the sources of allergens, house dust, diets, instructions for patients and other topics. Each chapter is provided with a concise summary and a list of references. In several cases the references cover many pages. The charts and the photographs serve their purpose nicely. Any one interested in allergic asthma will find this book a rich source of information.

Trauma in Internal Diseases, with Consideration of Experimental Pathology and Medicolegal Aspects. Rudolf A. Stern, M.D., assistant attending physician, City Hospital, New York. Pp. 575. Price $6.75. New York: Grune & Stratton, 1945.

In 1899 the first edition of Rudolf Stern's "Traumatische Entstehung innerer Krankheiten" was published by Gustav Fischer. The last major revision of the German edition was made in 1930 by Richard Stern, son of Rudolf. Although much of the present book has been taken almost verbatim from the German text, it is more than a translation. A considerable amount of new material, particularly from American authors, has been added. The most serious fault of the book arises from the fact that the author, like his predecessors, tends to designate as probable certain cause and effect relationships that would be better characterized as possible. In spite of this, the book is to be regarded as a welcome addition to the clinical literature dealing with the etiologic importance of mechanical injuries in the production of disease.

News and Comment

Appointments and Retirements.—James W. Jobling, Delafield professor of pathology and head of the department of pathology in the College of Physicians and Surgeons, Columbia University, New York, will retire from routine and administrative work on July 1 next.

Helen Ingleby has resigned from the professorship of pathology in the Woman's Medical College of Pennsylvania and will be pathologist of the Jewish Hospital in Philadelphia.

Andrew C. Ivy, professor of physiology at the Northwestern University Medical School, has been appointed a member of the National Advisory Cancer Council of the United States Public Health Service.

Alvin M. Pappenheimer, professor of pathology in the College of Physicians and Surgeons, Columbia University, New York, will retire July 1 next.

Jeff Minckler, formerly member of the department of pathology in the St. Louis University School of Medicine, has been named assistant professor of pathology in the University of Oregon Medical School.

Harry Pratt Smith, professor and head of the department of pathology in the University of Iowa, has been appointed professor and executive officer of the department of pathology in the College of Physicians and Surgeons, Columbia University, New York.

Death.—Hans Sachs, formerly professor of immunology at the University of Heidelberg, Germany, who was connected with Trinity College in Dublin, Ireland, where he had a fellowship, died on March 28, 1945.

Awards.—Edwin J. Cohn, professor of biochemistry at Harvard Medical School, is the first recipient of the Passano Foundation Award of $5,000. This foundation was established in 1944 to aid in research which bears promise of clinical application. The award was given Dr. Cohn in recognition of his work on blood plasma.

At a recent meeting of the American Foundation for Tropical Medicine the Richard Strong Medal for outstanding service in the field of tropical medicine was awarded to Rear Admiral Edward R. Stitt, former surgeon general of the United States Navy.

Fellowships.—The Permanente Foundation Hospital, Oakland, Calif., offers fellowships for clinical research, paying $225 a month plus maintenance. Requests for detailed information should be addressed to the fellowship committee of the hospital.

The Jessie Horton Koessler Fellowship of the Institute of Medicine of Chicago for the aid of research in biochemistry, physiology, bacteriology or pathology will be available on September 1. The stipend is $500 a year with the possibility of renewal for one or two years. Applications must be approved by the head of a department in the fields mentioned or by the director of a research institute or laboratory in Chicago, and it is stipulated that the recipient of the fellowship shall be given adequate facilities for carrying out the proposed research. Applications by letter with full information about the research should be sent to Dr. Paul R. Cannon, 950 East Fifty-Ninth Street, Chicago 37, before July 1 next.